

**Incidental motor sequence learning: Investigations  
into its cognitive basis and the effects of neurological  
impairment and treatment**

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## Abstract

To survive in a complex changing environment humans frequently need to adapt their behaviour *incidentally* from normal interactions in the environment without any specific intention to learn. Whilst there is a considerable body of research into incidental learning of sequential information there is still fundamental debate regarding its cognitive basis, the associated neural mechanisms and the way in which it is affected by neurological disease. These issues were explored, in normal participants and neurological patients, using manipulations of the Serial Reaction Task [SRT] in which participants gradually learn a stimulus sequence (usually screen locations) after responding to each item by pressing corresponding response buttons. The first two experiments (chapter 3) demonstrate that the specific metric used to quantify learning and the occurrence of highly salient repeat locations may inflate estimates of learning in tasks with increased motor demands. The next three experiments (chapter 4) examine whether a secondary (not directly behaviourally relevant) information source during the SRT facilitates chunking in memory and overall learning. In a spatial SRT task (specified by horizontal location), additional spatial information (vertical location) enhanced learning but a secondary perceptual property (colour) produced a cost. However, in a perceptual SRT a secondary perceptual property (colour) had no effect. The next study demonstrates that impairments of incidental learning in Parkinson's disease are partially reduced by administration of l-Dopa. Implications for models of striatal function and studies suggesting implicit learning is impaired by l-Dopa are discussed. Finally, the impact of Deep Brain Stimulation of the GPi is investigated in a population known to have only limited cognitive deficits relating to their illness (dystonia). Despite previous reports of impaired intentional learning in participants with a high genetic risk of Dystonia, there was no evidence for any impairment before or after stimulation. Implications across studies and future research directions are also discussed.

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## **Chapter 1**

### **I. An investigation of behavioural and neurological implications using the probabilistic Serial Reaction Time task to explore its specific contribution to our understanding of cognition**

#### **1.1. General introduction**

On a daily basis our brains are processing complex strands of information at a rapid rate (Hikosaka, Nakamura, Sakai, & Nakahara, 2002). We continue to formulate, consolidate and apply much of this information throughout our lives, always maintaining a capacity to learn more. As a species we have evolved to appreciate the value of consuming such information and knowledge. It is considered a key aspect of what we are as organisms. Expanding on this ability and utilising our capacity to do so have formed cognitive skills that are crucial for our interactions within society. Without doubt, cognition and our ability to learn are vital to our existence and beyond that, many people in society now pride themselves on enhancing these skills. There is a considerable industry in developing and marketing techniques to improve our memory or teach us to condense information in such a way as to enhance retention (Vernon, 2009). However, much of this is subjective and different techniques seem to work for some and not for others. This suggests that there is still much to understand about how individuals process information. One approach may be to investigate the complex processes that underlie learning and memory to gain further insights into how they contribute on a more specific scale.

The specific dynamics of the learning processes have been deconstructed in an attempt to identify how and what people learn when encountering a sequentially presented information series. Sequence learning has been the topic of debate for many decades, yet there remain many details, both specific and general, regarding its basis that are still the topic of much debate (Ashe, Lungu, Basford, & Lu, 2006; Doya, 2000; Hikosaka et al., 2002; Seger, 2006). At a basic level it seems that participants are able to learn through a series of habitual response processes, where information is consolidated to a degree where reaction times [RTs] decrease gradually due to anticipation before an automatic level of performance, is eventually achieved (Jenkins, Brooks, Frackowiak, & Passingham, 1994; Jueptner, Frith, Brooks, Frackowiak, & Passingham, 1997). The significance of better understanding this specific type of processing is that it sheds light on how we develop an understanding of information processing based on structural, perceptual, spatial and motoric features. Understanding these processes can help develop our knowledge of how our brains direct us based on our environment and what specific details are harnessed to aid our performance.

### 1.1.1 Sequence Learning Tasks

Sequence learning is the processing of a structured order of events that are often presented visually (Cleeremans & McClelland, 1991; Nissen & Bullemer, 1987) but can also be presented through auditory tones (Koch & Hoffmann, 2000a). Learning of these sequences can take place incidentally (when participants are not told of the sequence but demonstrate learning through habitual processing) or intentionally (when they are instructed to learn the sequence; see section 1.3). In some cases, sequence learning can be primed through auditory tones (Dennis, Howard, & Howard, 2006) or even tactile stimulation (Abrahamse, Jiménez, Verwey, & Clegg, 2010) but typically they share the same feature of signalling a specific motor response through a display monitor based on a target stimuli. Participants are often instructed to respond to the target as quickly as possible by pressing a corresponding button on a response box, keyboard or by moving a lever. The stimuli themselves can involve geometric shapes, colours or a simple arbitrary symbol such as an “x”. However, the display itself can vary quite significantly in design. Some tasks for example involve a circular array of possible locations like a clock face (Carbon et al., 2003; Ghilardi et al., 2003), others employ objects appearing in the four corners of a display monitor (Lungu, Wächter, Liu, Willingham, & Ashe, 2004; Mayr, 1996), lever pulling experiments (Hikosaka, Miyashita, Miyachi, Sakai, & Lu, 1998) and some involve a single location appearing in a central location on the screen (Willingham, 1999), responses to which are determined by digits (Koch & Hoffmann, 2000a; Willingham & Goedert-Eschmann, 1999). Nevertheless, the most common presentation of sequence learning experiments, involves four boxes appearing horizontally on a display monitor, with a symbol appearing in any one box at a time (Nissen & Bullemer, 1987). This particular task is known as the Serial Reaction Time [SRT] task and was originally introduced by Nissen and Bullemer (1987) who compared RTs for a deterministically presented sequence of locations (D-B-C-A-C-B-D-C-B-A or 4-2-3-1-3-2-4-3-2-1) with a random sequence performed by a control group. It was discovered that while there was a small superficial decline in RTs for the random sequence, participants became significantly faster at responding to the 10 item series. The authors argue that evidence for this learning is present by the latter half of the first block (Nissen & Bullemer, 1987). An analysis of all ten cycles in block 1 revealed significantly faster RTs by the seventh cycle (by around trial 70) compared to the comparable stage in the random condition. These findings not only demonstrate that learning of a sequence of information is possible but that evidence of this can present itself at a very early stage.

In a second experiment the authors advanced their findings by replicating the sequenced task under the exact same parameters as in experiment 1, whilst also introducing a further

condition where participants were to learn whilst performing a secondary task. In this case, participants heard either a low or high pitched tone presented simultaneously with each sequence location. They were instructed that in addition to responding to the changing locations they were also to count the number of low pitch tones in each block. These were again performed for both structured and random sequences. Results revealed that when performing the tone counting task although RTs did decline there was no difference between the two sequence structures. This is perhaps surprising in the random condition as the previous experiment had not detected a significant decline in RTs. The authors argue that this may be due to participants' simultaneously learning features in both tasks. Therefore, faster RTs are comprised of practice at counting the tones and responding faster to the sequence. However, the magnitude of learning in the dual task sequence learning condition was still less than for the sequence on its own, which denotes a cost for the simultaneous performance of both tasks. A third experiment compared learning between two groups where both began by performing the same simultaneous sequence and tone counting task. This was followed by a transfer stage where tones were removed for both conditions. However, during this transfer stage, one group continued to perform the same sequence and the other a random sequence. The authors identified that the random transfer incurred a RT cost whereas those performing the same sequence produced gradually faster RTs.

Responses to these locations are often dependent on the specific task. In many cases, participants are instructed to use their index fingers on both hands or the index and middle fingers to respond. In other cases only one effector is used and the response is made by four fingers of the dominant hand. Of course this is not the case in other sequence learning experiments where responses are made with levers.

In most cases, the symbol remains in the same location until a response is made. However, in some designs, participants are required to respond within a time limit. Once this has been successfully achieved, the stimulus shifts to another location where again participants are to make a response. However, if unsuccessful, the stimulus remains on the screen until a correct response is provided. As mentioned, it is thought that through habituation of the sequence, participants gradually learn to anticipate the structure and develop faster RTs as the task goes on.

### **1.1.2 Intentional vs. Incidental**

Both incidental and intentional sequence learning have been studied. Among other techniques intentional learning has been studied by a paradigm where participants have been informed that they are responding to a sequence of locations (Carbon et al., 2008; Jueptner,

Stephan, et al., 1997). By contrast, incidental learning experiments do not involve divulging the presence of a sequence to participants (Nissen & Bullemer, 1987). Instead, participants are required to treat the task as a simple reaction time exercise where they are instructed to respond to locations as quickly and accurately as possible. In both cases, it is thought that learning of the sequence can be obtained through training as consistent exposure to the sequence encourages its consolidation (Jenkins et al., 1994; Jueptner, Frith, et al., 1997; Jueptner, Stephan, et al., 1997). How this learning is reinforced and what specific features are used to do so is an issue of some contention (see chapter 4). Nevertheless, the specific mechanisms required to perform these tasks are potentially different. One can argue that intentional learning is a goal orientated form of information processing as participants are given clearly defined instructions to focus towards identifying a fixed structure amongst the stimuli presented. By contrast, incidental learning is a process relying on self initiated anticipatory responses as a result of habituation to the sequence. It is surprising, therefore, that some researchers have failed to distinguish between the two methodologies investigating very different forms of learning (Clegg, DiGirolamo, & Keele, 1998). This is particularly valid as some studies have demonstrated that incidental and intentional sequence learning are processed in different ways (Clegg et al., 1998; Keele, Ivry, Mayr, Hazeltine, & Heuer, 2003).

The significance of the two methodologies is not in question as both have their own uniquely specific advantages based on what it is the experimenter aims to investigate. However, the current thesis focuses upon investigations using an incidental approach to measuring learning as it allows me to identify specific principles in the design of sequence learning experiments that contribute towards unconscious learning.

Studies have previously reported that the presence of awareness can interfere with incidental learning (Ashe et al., 2006), which is an effect with several interpretations. First, it is possible that learning is a flexible process, based on several learning systems that can potentially operate independently of each other (Willingham, Wells, Farrell, & Stemwedel, 2000; Willingham, 1999) and in parallel (Mayr, 1996) in order to consolidate information. Probabilistic classification learning paradigms (Knowlton, Mangels, & Squire, 1996) exemplify this perspective as such tasks involve participants being aware that they must learn a pattern in the task to perform correctly despite not being able to explicitly explain what they have learned. Nevertheless, in later stages of the task, evidence of incidental learning can be accompanied by awareness of the rule based system too (Knowlton et al., 1996; Poldrack & Packard, 2003; Poldrack et al., 2001). Imaging during these experiments revealed striatal activity during implicit processing and Medial Temporal Lobe activity for



explicit sections at the end of testing where they are asked to rate stimuli based on their importance, regardless of whether participants are able to explain the rule or not. This implies that there are two distinct areas of the brain that attempt to fulfil learning based on whether participants are learning while not having to explain their choices and when they are, forced to explain their judgments. Although in some cases they can interact, it is better to maintain a focused perspective that approaches the two in isolation as it is still poorly understood, when and how the two can be successfully applied in unison.

Another view is that incidental learning engages a form of processing that is perhaps both motorically as well as perceptually different to those required for intentional learning. Studies have often addressed the issue of automatic performance and consolidation of information in sequences on which participants have trained compared to those that are new to them. In most cases they find a consistent range of activity beginning in the dorsolateral prefrontal cortex [DLPFC] for new sequences that gradually diminishes with increased presentations and is eventually superseded by activity in the Basal Ganglia once learning has been consolidated (Jenkins et al., 1994; Jueptner, Frith, et al., 1997; Jueptner & Weiller, 1998). As participants are aware of a sequence before they even begin the experiment, it is probable that they begin with the aim of forming a strategy or developing one throughout training. Potentially this could even result in slower RTs to begin with to that of an incidental paradigm as they are not performing automatically and quickly but attempting to find and remember a pattern. Consequently, performance maybe tentative and focused on specific responses instead of being performed automatically and in an intuitive response selection process that may provide faster and more sensitive response biased RTs. Furthermore, it should be highlighted that any awareness in this case does not constitute a definitive understanding of a rule but only that a rule exists. In this case, deviations from the rule may not be so costly. On the other hand, an automatic and incidental approach may involve a more rapid series of engagements based on intuitive responses. It may be expected that incidental learning is less affected by changes to the sequence structure as participants are training on simply making fast responses. Indeed when comparing incidental and intentional learners, it has been discovered that intentional learning shows a greater improvement (Rüsseler, Hennighausen, Münte, & Rösler, 2003) although the representation of learning in the two methodologies are said to be qualitatively different (Curran & Keele, 1993). However, it may be possible to address more complex rules as any learning is incidental and so participants are constantly engaging automatic responses regardless of the complexity of the sequence structure as they are unaware of its' presence. To put it simply, learning a complex task intentionally encourages participants to attempt to understand the complexity

of its' structure whereas learning the same task incidentally requires no such understanding as participants' are not aware of its' presence. It is therefore possible that under the right circumstances a simple or complex task learnt incidentally could result in similar or at least more sensitive levels of learning.

Many studies have in the past assumed incidental and intentional learning to be similar and taken results from both methods as reflective of the same form of processing. For the purposes of the current investigations and particular aspect of learning which they address, the incidental methodology will be used for all studies to try to tap an automatic level of performance. As well as providing consistency throughout all experiments, the incidental approach includes interesting implications for investigating learning. First, participants are unaware that they are participating in a sequence learning experiment. This reduces knowledge of the purpose of the experiment influencing their performance. Second, awareness becomes a feature of independently applied knowledge and adaptation to the task. As participants are not aware of the sequence, it is entirely left to their own abilities to identify order in the task. Awareness therefore becomes a subjective principle based on entirely the participants' own engagement with the task. Intentional tasks may on the other hand encourage participants to identify sequence structures and detract from the primary purpose of the task. In this sense, awareness testing in intentional tasks is more a feature of how successful participants have been in deliberately identifying and isolating the sequence, whereas incidental tasks reveal how well they can recall information that they may only be conscious of at the end of testing when the experimenter informs them of it (i.e. awareness might only form once they have been told of the existence of a sequence). To this extent, awareness in an incidental task may be less consequential as any explicit knowledge may still have only occurred after the main task and only when the true parameters of the experiment are revealed. Finally, as mentioned before, it allows us to approach experiments with greater potential for manipulating its design. As participants are not aware of the tasks purpose, one can not only increase complexity but also include extra features without undermining others. For instance in a case where participants are aware that a sequence is present, it may be detrimental to provide secondary dynamics as they may inherently contradict what they have been told to look out for. However, if participants are completely naïve to the formation of the task, any specifics in the presentation should appear to be uninformative. Due to this, one may afford the option of increasing the technical complexity and load of the task.

### 1.1.3 Standardisation of sequence structures

The sequence itself and the measurement of learning have also been explored using different methods. The format of the sequence can often depend on the particular focus of the experiment; for this reason, one often comes across paradigms that have employed quite unique sets of sequences. The sequence length for example, can vary from being four to twelve items long, with some experiments involving repetitions of locations and others not. Cohen, Ivry, and Keele (1990) were amongst the first to identify the significance of patterns in sequence structure by providing a distinction between ambiguous and unique sequence transitions. A unique sequence involves items that follow first order transitions, for example, if the digits 1, 2, 3 and 4 are taken to denote spatial locations from left to right, a sequence of locations such as, 1 2 4 3 would constitute a unique set of location transitions as 2 is always predicted by 1, 4 is always predicted by 2 and so on. However, ambiguous sequences do not consist of any direct transitional relationships. Instead, they are dependent on higher order information so that in a sequence such as, 1 3 2 3 1 2, each location is followed by two possible alternatives. In a further development Cohen and colleagues (1990) combined features of unique and ambiguous structures to create hybrid sequences. In this case the sequence consisted of both first and higher order information (e.g. 1 1 4 2 3).

Many have chosen to tackle sequence learning using these standardised formats developed by Cohen and colleagues (1990) and further evolved by Reed and Johnson (1994). Using Reed and Johnson's (1994) sequence pattern, a range of fixed, twelve item sequences can be constructed, each governed by the principles that there should be four possible locations, with each location occurring three times and never repeating consecutively. Reed and Johnson sequences employ a similar formation to that of Cohen and colleagues (1990) unique structures. Reed and Johnson's (1994) Second Order Conditional [SOC], sequences maintain the rule that each location should be preceded by a different item on each of the three instances that it occurs. Subsequently, participants who are aware of the sequence will never be able to tell where the next location in the experiment will be based on a single location (as all four possible locations are preceded by each of the three remaining possibilities) but should always know the next location by being presented with no more than the last two locations of the sequence. This is because each couplet in the sequence can only occur once, in the twelve locations and so by due process, the same is true of each triplet. Therefore, at any point, those who know the sequence can always tell the next location based on the two previous items. Therefore, Reed and Johnson (1994) sequences are complicated structures with variable patterns of locations to make it difficult for participants to identify

the regularities in their formation but are nevertheless fixed structures based on definable rules.

#### **1.1.4 Deterministic vs. probabilistic sequence presentation**

Primarily there are two main methods that can be adopted when presenting the sequence structure. Perhaps the most common of these methods are deterministic sequences (Koch, 2007; Shanks, Wilkinson, & Channon, 2003; Stefaniak, Willems, Adam, & Meulemans, 2008). In this case, the chosen sequence is repeated continuously on a loop without interruption. Participants are expected to learn the sequence through repetition. However, in some cases, particularly when the experimenter desires the sequence to remain incidental, a tone counting task can be incorporated simultaneously with the sequence to draw some attention away from the task and minimise the likelihood of awareness. Often this involves participants counting how many tones they have heard (Cohen, Ivry, & Keele, 1990; Curran & Keele, 1993; Nissen & Bullemer, 1987). Learning in a deterministic paradigm is frequently measured by comparing RTs for a random block trial (presented towards the end of the task) with those for blocks of trials with the learned sequence. Often the random block will be presented as the penultimate block before returning to the original deterministic sequence for the final block. It is expected that for learning to have taken place, RTs will become faster across blocks where the deterministic sequence has been used but slow during the random block. This demonstrates the participants' ability to habitually enhance their performance on the repeating sequence as the task progresses due to incremental learning. Increases in RTs for the random block represent the abolition of any anticipatory responses as participants must perform clusters of responses that they are not familiar with. Consequently, RTs to these trials are significantly slower. To further reinforce the evidence that learning has taken place and that this has been consolidated, a final sequenced block is introduced after the random block where it is often noticed that RTs once again return to a level similar to that preceding the random. Learning is then calculated through a comparison of the mean RTs from the random block and the overall mean RTs from the blocks immediately preceding and following it. Significantly slower RTs in the sequenced blocks before and after the random block are evidence for sequence learning.

There are however, several limitations with deterministic sequences that complicate the interpretation of their results. To begin with, it can be argued that the repetition of the sequence over a prolonged period of time may be too perceptually and motorically distinctive to remain incidental. Consequently, participants may identify a pattern in the sequence which would alter their strategic approach during the experiment. Although this in

itself raises interesting questions, it is perhaps undesirable for one who wishes to investigate the impact of subtle characteristics of the sequence itself and the significance that has on learning. For example, if there are secondary cues or aspects to the sequence that are thought to be relevant to a participants' performance, any identification of the existence of a sequence may increase the probability that this additional element will be noticed by participants. Should the priming of this secondary information be important to the results of the experiment, the importance of it remaining incidental throughout testing is clear. Additionally, at a more simplistic level, if the objective of an experiment were to identify learning in the absence of awareness for any particular reason, a deterministic sequence may not be the ideal solution. Indeed, authors have argued that there are better solutions to avoid this (such as probabilistic designs) (Howard & Howard, 1997; Song, Howard, & Howard, 2008; Wilkinson & Jahanshahi, 2007). Another disadvantage may be the use of a single random block. Considering that it is expected that participants will begin to anticipate responses and consolidate this intuition as they progress through the task, the introduction of an entirely different pattern of locations at a point where learning should be at its strongest may further illustrate the structure of the sequence to participants. Not only may this introduce an additional element of RT cost to slower responses in the random block, it may also interfere with performance on any subsequent awareness measures. Essentially, participants may therefore, at an early stage of testing, become aware of a pattern (which they have not been told of) and have this awareness further reinforced by the abolition of the sequence in the random block. This implies that participants will have a substantial period of time where they can deliberate on (i) whether there is any significance to why they were not informed of the sequence, (ii) whether there is anything specifically important about the sequence itself, (iii) when the sequence is removed, whether there is any significance to the locations presented in the random block and finally, (iv) whether the test is indicative of something more cognitively or intellectually probing than a simple RT test. All of these factors can consequently alter the meaning of the results for both the RT and awareness measures as well as alter goal directed behaviour.

In recent times, an increasingly popular approach to testing incidental sequence learning has been the use of probabilistic sequences. Unlike deterministic sequences, probabilistic sequences vary in presentation, meaning that no one continuous cycle of locations is present. Instead the sequence is systematically interrupted throughout testing so that participants cannot become accustomed to any predictable repetitions. Due to this, the sequence becomes even more difficult to detect and supports the main goal of maintaining incidental learning. Experimenters have adopted different methods in presenting probabilistic sequences, with

some continuing to measuring learning through a random block towards the end (Deroost & Soetens, 2006a) or by simply comparing RTs from grammatical with non grammatical sequences (Cleeremans & McClelland, 1991). However, a useful development in the design of probabilistic sequences was first proposed by Schvaneveldt and Gomez (1998), who adapted Reed and Johnson's SOC sequence structures to include probable and improbable trials. The percentages applied to the structure can vary from 80/20% or 90/10% (Schvaneveldt & Gomez, 1998) or even 85/15% variability (Shanks et al., 2003; Wilkinson & Jahanshahi, 2007; Wilkinson & Shanks, 2004). This means that 85% of the time (for the latter example), participants will respond to locations that are taken from the probable SOC and the rest of the time from an improbable parallel SOC. A crucial feature of the design is that participants do not continuously perform the same repeating sequence; instead, the structure is periodically disrupted, meaning that anticipations and expectations will always be contradicted at some point. Due to the sporadic presentation of the improbable trials across all blocks, learning can be measured all the way through testing. To do so, mean RTs are taken separately for probable and improbable trials across all blocks and compared against each other. It is expected that for learning to have occurred, RTs to probable trials will be significantly faster to those of improbable locations. Schvaneveldt and Gomez's (1998) approach replicates the same effect of using a random block but eliminates the more generalised effect of presenting interruptions in a single block. As a result, the significance of the improbable trials, presented systematically across blocks is more difficult to detect and therefore, less likely to become a consequential feature in the task. The approach also allows one to monitor differences to probable and improbable trials throughout testing, meaning that one can compare stages of learning. Therefore, the use of Reed and Johnson (1994) SOC sequences with Schvaneveldt and Gomez (1998) probabilistic trials, removes the repetition of deterministic methods as well as the use of a single random block, thus improving the potential for tests to remain incidental.

### **1.1.5 Incidental learning and awareness**

Considering that this thesis has, at least partly, justified the use of probabilistic sequences based on the likelihood that participants will remain unaware of the uniform pattern of repeating items, it is important to explain how this impacts on the nature of learning that is of interest. Beyond the basic principle of a distinction between incidental and intentional, one must draw a line between the significant differences in incidental and implicit learning where the latter refers to learning which has taken place in the absence of any awareness. Probabilistic classification learning is one example of where incidental and implicit formulations of a task can collide, particularly in the Weather Prediction Task [WPT]

(Knowlton et al., 1996; Poldrack et al., 2001; Wilkinson, Beigi, Lagnado, & Jahanshahi, 2011; Wilkinson, Lagnado, Quallo, & Jahanshahi, 2008). In this paradigm, participants are asked to arrive upon a decision of “rainy” or “sunny” weather based on anywhere between one to four tarot cards. After each response, participants are then given feedback on each trial to inform them of whether they were correct or not. In between trials (after 25 or 50 trials), participants are also probed for their judgment on each card separately in order to gauge how accurately they are explicitly rating a card. However, participants are not informed of the precise nature of the task, only that they are to make a prediction based on the cards they see. Unbeknown to them, each card is associated with a probabilistic outcome where two of the cards are strongly (80%/20%) and the other two weakly (around 60%/40%) associated with an outcome (Poldrack et al., 2001; Wilkinson et al., 2011, 2008). It is considered that participants who seem to perform well on the task but demonstrate poor explicit understanding are implicitly learning that paradigm. However, there are several crucial discrepancies between probabilistic sequence learning and probabilistic classification learning. To begin with, learning on the WPT can be argued to be goal orientated as participants are informed that they are to achieve a certain outcome based on the cards presented. Immediately, this signifies an objective that many participants will surely assume will be meaningfully associated with the cards. This is further reinforced in the explicit stage, where participants are asked to openly attribute a specific rating towards each card to indicate whether it is more likely to result in “rainy” or “sunny” weather. Although an attenuated explicit score accompanied by a relatively high implicit performance would indicate that participants have learnt in the absence of awareness, learning of the task is not necessarily incidental in the same way as it is in sequence learning tasks. In this thesis for learning to be considered purely incidental, participants should not be aware of the fact that their responses are fulfilling a goal, other than for the secondary non-learning task (e.g. responding to a stimulus as quickly as possible). Instead their behaviour should be reinforced internally through complex processes that infer information in the absence of awareness. On the WPT, this is immediately compromised when participants are told that there is a correct or incorrect decision and provided feedback. It has also been established that performance on the paradigm can be modulated by the level of feedback that they receive, implying that performance is not only governed by the fact that there is something to be learnt but that their awareness of their own performance can influence how well they do.

The fact that participants can perform the WPT at a high level while not being explicitly able to explain their judgments is consistent with reports that in some cases awareness is not established during sequence learning (Cleeremans, Destrebecqz, & Boyer, 1998; Song,

Howard, & Howard, 2007). In this case, participants are aware that there is something to be learnt but nevertheless must establish it themselves, as is the case in the WPT. Furthermore, it is possible that identifying a sequence or any sort of meaning in a task (even if they are not informed about it) can alter the participants' goal directed behaviour. This distinction between goal directed and incidental learning can have implications on a range of approaches, including when one wishes to probe for participants' ability to use very complex strings of information in a relatively short period of time. This is particularly important as one can speculate that this level of processing has a greater chance of succeeding when participants are performing incidentally (Song et al., 2008). To this extent, the level of awareness, or the ability to represent it is not necessarily the crucial issue, but instead it is the behavioural implications of understanding that there is more to the task than simply responding to a series of locations. Indeed, Cleeremans and McClelland (1991) have argued that the degree to which an individual is aware based on their measures does not effect to degree to which they learn implicitly, which implies that learning and awareness can exist independently of each other. However, this thesis maintains that the specific behavioural implications of an incidental or intentional approach and the consequence of participants becoming aware during a task are crucial.

## **1.2. Developments in sequence learning**

Now that research is beyond the early days of sequence learning experiments and the development of the SRT paradigm, experimenters have begun to explore more detailed implications of the paradigm (Koch & Hoffmann, 2000a, 2000b; Shanks et al., 2003; Willingham & Goedert-Eschmann, 1999). Experimentally, these developments have taken several directions. Some have chosen to explore and question the specific nature of the information learned during sequence learning and how it is acquired. This has included experimental studies regarding sequence structures (Cleeremans & McClelland, 1991; Cohen et al., 1990; Reed & Johnson, 1994) as well as Response to Stimulus Interval's [RSI] (Destrebecqz & Cleeremans, 2001; Wilkinson & Shanks, 2004), concurrent or dual task learning (Jimenez & Mendez, 1999; Nissen & Bullemer, 1987), effector specific learning (Perez et al., 2007; Willingham et al., 2000) and Stimulus-Response [S-R] compatibility effects (Deroost & Soetens, 2006b; Koch, 2007). As well as this, experiments have employed sequence learning tasks to identify brain activation using fMRI, PET, EEG and TMS. This information has also been used to infer performance capabilities in neurologically impaired populations. Together, these studies have begun to provide an insight into how learning materialises and the areas that are important for the successful performance of sequence learning.



### **1.2.1 Multiple Effectors**

Specific investigations regarding the particular elements of sequence learning tasks that are being learnt have largely divided attention to the contribution of motoric or perceptual features. It has been argued that it is possible that individuals are not learning the sequence itself but that the repetition of finger movements throughout training are resulting in motor associations that aid learning (see Schwarb and Schumacher 2012 for a review). In order to investigate this, experimenters have devised a series of studies aimed at manipulating S-R mapping. Willingham (2000) investigated this effect using a cross effector (participants cross hands when performing the task) model where participants responded to items appearing in one of four locations on a display. In the first instance, participants were asked to perform a sequence using the index and middle fingers of both hands. A spatially compatible S-R mapping was incorporated so that the middle finger of the left hand would respond to items on the far left and index finger of the left hand to items appearing second from the left, etc. After a period of training, participants were instructed to cross their hands, in order to disrupt S-R compatibility. At this stage, some participants performed the same sequence with a different mapping (index finger of the right hand responds to items on the far left), while others performed a different perceptual sequence which was specifically designed to recreate similar finger movements (Willingham et al., 2000). It was discovered that at transfer, learning was only maintained when the perceptual sequence was kept the same. However, Willingham and colleagues (2000) do not consider this to be reflective of perceptual learning but what they describe as learning response selections. This means that participants are learning the response modality.

However, others have not accepted the response selection hypothesis and instead favoured a view that perceptual features are being learnt. For example, Cohen and colleagues (1990) trained their participants on a sequence using responses taken from four fingers of one hand. After 10 blocks of training, the authors changed these instructions to involve responses using just the index finger whilst the stimuli remained the same. Results from this study indicate that learning did not change due to switching response effectors; leaving perceptual features of the task as the remaining central feature (see section 1.3 for more detailed review of stimulus based learning).

### **1.2.2 Tone counting implications for sequence learning**

Many experiments have investigated sequence learning whilst participants are asked to count tones presented concurrently with the visual sequence, which is intended to either mask awareness (Song et al., 2008) or investigate dual task processing (Cohen et al., 1990; Curran

& Keele 1993). However the complex interactions of tone counting and sequence learning are unclear. For example, some researchers have reported that it impairs sequence learning (Nissen & Bullemer 1987), has no effect (Cohen et al., 1990) or simply masks its presence (Frensch et al., 1998). It is suggested that the reason for impairment is due to tone counting requiring more attention (Nissen & Bullemer 1987; Curran & Keele 1993; Jimenez & Vazquez 2005), although this has been challenged. For example, Stadler 1995, demonstrated that changing the RSI to involve 400ms or 2000ms pauses was sufficient to produce learning to a similar degree to that of another condition where concurrent tone counting was performed. They argue that this is consistent with a view that tone counting alters organizational components of sequence performance (Stadler, 1995). Therefore, tone counting is not altering attention but breaking the organization of sequence presentations.

This model has been developed more recently by Schumacher & Schwarb (2009) who devised a tone response task where participants were asked to verbally respond to tones whilst performing visual sequence learning. The authors explain that when participants make simultaneous motor (to the visual stimuli) and verbal (to tones) responses, learning of the sequence was not present. However, when tones were presented with a 750ms delay and verbal responses were consequently made after the visual stimuli appeared, learning was present (Schwarb & Schumacher, 2009). It is perhaps the integration of these resources that are responsible for concurrent sequence learning with tone counting (see Schwarb & Schumacher 2012 for a review).

Another perspective is that sequence learning is reliant on the ability to develop and maintain an automatic level of performance. One particular group have argued that it is this ability to perform automatically that can influence the degree to which one can learn implicitly (Frensch, Buchner, Lin, Loewe, & Experiments, 1994; Frensch, Lin, & Buchner, 1998; Frensch, Wenke, & Riinger, 1999). Using ambiguous sequences, Frensch and colleagues (1994; 1998) have demonstrated that concurrent tone counting does not abolish learning but masks its presence. They demonstrate that at transfer, when tone counting is removed, participants are nevertheless able to demonstrate that they have learnt.

### **1.2.3 Attention and load**

The influence of additional load on sequence learning has also been investigated. For example, Rowland and Shanks (2006) designed an SRT task incorporating multiple sequences presented concurrently. Participants were under instructions to respond to the primary sequence whilst ignoring responses to the secondary locations that were presented above (Rowland & Shanks, 2006a). However, after a period of training on the primary

sequence, participants were instructed to also respond to the secondary targets. It was discovered that RTs to the secondary sequence were similar to those of the primary locations. It would appear, therefore, that participants were able to divide attention, even when instructed not to and perform at a high level on a secondary source of information. In a second series of experiments, the same authors investigated the impact of distractors on learning (Rowland & Shanks, 2006b). This involved an attentional low load group performing under similar conditions to the previous experiment and a high attentional load group that were also exposed to additional red squares and green circles presented below the primary and secondary sequences to capture their attention. They discovered that regardless of load, learning was apparent in the primary sequence but only the low load group demonstrated learning in the secondary sequence. The authors conclude that incidental learning under these circumstances may act like a filtration system, reducing the amount of highly concentrated information being processed at any one time (Rowland & Shanks, 2006b). For this reason, there may be an upper threshold on the capacity to process supplementary items beyond which learning of additional information is deficient. (Lavie & Tsal; Lavie 1995; Lavie et al., 2004)

Rowland and Shanks' (2006b) argument is not dissimilar to that of Cohen and colleagues (1990), who claim the associations between items in a sequence structure can be critical for the formation of learning. They discovered that their own manipulation of unique, ambiguous and hybrid sequences could all be learnt under single task constraints. However, learning was only apparent in unique and hybrid sequences when dual learning constraints were introduced. The authors claimed that their findings were consistent with a view that learning under distraction is facilitated by sequences that incorporate unique associations whereas ambiguous structures require a hierarchical processing of information due to the greater levels of attention required. They suggest that their study involves two distinct learning mechanisms (Cohen et al., 1990). The first forms associations based on transitional patterns such as unique sequences and can be performed with distractors but would not be able to support higher order transitions such as the case in ambiguous or SOC sequences. The second, on the other hand, requires hierarchical processing to constrain parsing of certain items to allow one to account for the more complex SOC properties as opposed to a simpler rule that each item predicts the next. In this case, parsing must account for the fact that 1 can be followed by 2, 3 or 4. The authors also admit that it is possible for hierarchical processing of unique and hybrid structures but they favor the former principle (Cohen et al., 1990).

Another perspective regarding sequence structure and learning has been to observe frequencies associated with each items presentation. It is thought that higher frequencies in item presentation may result in learning due to greater facilitation of their occurrences resulting in habitual response priming (Lungu et al., 2004). In a series of experiments, Lungu and colleagues (2004) sought to investigate the effect of (i) mapping, where responses were designed to occur either on the same or opposite side of the screen with equal transitions, (ii) perceptual, where stimuli presented on one side on significantly more occasions than the other, and (iii) movement, where a particular finger was used more than another, all in response to dominant stimuli. The authors discovered that regularities in the presentation of stimuli were responded to faster in the mapping and perceptual conditions but not in the movement condition. Nevertheless, less dominant stimuli produced slower RTs for all three conditions. Results suggest that when stimuli are salient, consistent motor priming does not facilitate better learning. This may be in contrast to Willingham and colleagues (2000) assertion that response locations are responsible for sequence learning as Lungu et al. (2004) seem to suggest that the response location is not necessarily vital as long as visual priming of stimuli is strong enough.

If this is the case and motor learning is weakly associated with performance on sequence learning tasks in Lungu and colleagues (2004) specific paradigm observation based learning may prove to be a more effective manipulation. A recent study reported that three observation groups (with no direct motoric stimulation) who (i) observed the sequence on the screen, (ii) observed an actor perform the sequence, or (iii) observed an actor as well as the sequence on a screen, were able to learn a sequence as well as a final group who (iv) actually performed the sequence (Bird, Osman, Saggerson, & Heyes, 2005). They concluded that action observation can elicit a similar learning process to that of actually performing the equivalent actions (Bird et al., 2005). This would suggest that at the very least, the motoric component of the SRT is not critical in order to demonstrate learning. Though, the visual stimuli may be activating motor areas possibly via mirror neuron systems (Keysers et al., 2003).

Perhaps some of the clearest evidence for stimulus based learning comes from observational studies where participants who are simply watching a sequence of location and not responding to them can demonstrate learning. Howard et al., (1992) was amongst to first to demonstrate this. The authors identified that participants' who were asked to first observe a sequence and then transfer onto performing it with motor responses learnt the sequence as well as a separate group who performed it throughout. However, a later study by Willingham (1999) developed the argument to demonstrate that it is only those who obtain awareness of

observational tasks that learn. In his study, Willingham (1999) removed observational learners who had obtained awareness and discovered that learning was not present for the rest. Failure to demonstrate observational learning has also been reported by others (Kelly, Burton, Riedel, & Lynch, 2003; Reiss et al., 2005). However, using a probabilistic version of SRT task, Song and colleagues (2008) have addressed these issues. They argued that failure to find learning in Kelly and Burton's (2001) may have been due to participants' not engaging with the experiment and consequently not attending to the task. Song et al., (2008) resolved this in the second experiment of their paper by asking participants to report patterns that they may have detected at the end of each block. It is argued that learning under these vague instructions and the use of probabilistic sequences should be enough to maintain implicit learning. This was confirmed by their results suggesting that participants' were able to learn without awareness of the sequence (Song et al., 2008). This study implies that observational learning can occur, even with probabilistic sequences. Nevertheless, the strength of this learning is exposed by an initial experiment where participants are placed into incidental and intentional learning groups. In this case, participants in the intentional group were asked to declare the order of the sequence after each block. Alternatively, for those in the incidental group, participants' were asked to count the number of red targets that appeared (up to 7). The authors report that neither incidental nor intentional participants were able to learn with observation. It is believed that the colour cues used may have interfered with the acquisition of learning. As this was removed in their second experiment, learning was facilitated under the less demanding constraints.

#### **1.2.4 Spatial and perceptual implications**

Based on the findings of previous researchers, it is interesting to consider what constitutes significant information and to what extent additional variations can aid learning. It has been discovered that additional load can be sufficient to disrupt learning under certain circumstances but not others, and that the reason for this depends on the specific sequence structure used and the degree to which the distractors are salient. However, the effect of spatial features, are perhaps less well developed in sequence learning studies, particularly when using probabilistic designs. Furthermore, what constitutes attention or load is not so well defined. For example, probabilistic sequence learning can involve locations from probable (85%) and improbable (15%) sequences (Wilkinson & Shanks, 2004). In some cases, this may be referred to as an additional load on attention as participants must adjust to the distraction created by improbable locations, at least if they are becoming aware of the sequence. However, as the secondary feature is incorporated within the sequence, participants are not necessarily aware of its importance. In other words, they are not aware of

the fact that there is something additional to the task. This leads to an interesting question of whether additional information or load would have an effect on cognitive processing if it were more directly tied to the primary task. For example, if participants in the Rowland and Shanks (2006) experiment were not as perceptually affected by the distractors presented and instead an equivalent level of complexity was introduced as part of the primary sequence, perhaps they would not have been affected by a high load condition. This view may be contradictory to previous research claiming that the extra features would be more difficult to ignore if they are in the primary task (Lavie & Tsai, 1994).

The precedent to this possibility was presented by Schmidtke & Heuer (1997) who demonstrated that a potential reason for dual task performance disrupting sequence learning was due to the integration of the multiple tasks used. In an initial experiment, they demonstrated that incidental sequence learning was present when a six item sequence was performed alongside a concurrent six item go/no-go tone counting task. However, learning was not as strong in another condition where participants performed the same six item sequence but concurrent tones were played in a five item sequence. The asymmetry between the number of stimuli led to a far greater number of combinations of the two stimuli (6-element visual and either 6 or 5-element auditory respectively). The role for attention in these exercises is revealed in a third experiment where Schmidtke & Heuer (1997) demonstrate that this learning is dependent on participants' performing both visual and auditory tasks when they are present. They claim that those who are instructed to simply perform the visual sequence and not count tones do not demonstrate learning. In this sense, integration of available sensory stimuli when presented, seems to be vital for learning, even when it has been shown that secondary features (in this case tone counting) are not necessary for sequence learning (i.e. visual sequence learning can occur independently to secondary tone counting).

However, Schmidtke & Heuer's (1997) task again involves two separate concurrent tasks, meaning that it is yet to be understood how integration of two components into one overall task will affect incidental sequence learning. This is even more uncertain in probabilistic sequence learning using the SRT.

Perhaps more intriguing than this, is the question of whether learning can actually be enhanced through this method. As has been demonstrated, research has revealed that learning can be achieved and maintained under additional resources but whether there are specific features that can improve performance is unknown. Furthermore, the specific features that may enhance learning are not so well understood. Research has revealed that

motor components may not be as vital as previously believed but the specific perceptual components that are involved are not clearly defined.

For example, Koch and Hoffman (2000) have reported that sequence learning is not dependent on multiple special cues. Instead, participants are capable of learning a sequence of items presented in a single location based on a trained S-R mapping where digits appearing in the display are mapped to a particular finger response. In this case, spatial dynamics are removed and learning must take place under associations between the stimuli presented and the particular finger it triggers. However, what remains unclear, and indeed what Koch and Hoffman (2000) state themselves, is whether there remains something special about spatial presentations of information that enhances learning in these paradigms. Nonetheless, it remains possible that spatially presented sequences of information may present a capacity to present more complex sequence (a proposal directly addressed in chapter 4 of the current thesis).

### **1.2.5 Spatial compatibility**

S-R compatibility refers to the correspondence between stimuli and response mappings, meaning that an experiment involving a response rule that violates what may be considered to be the stimuli's logical spatial or perceptual link with the particular response selection is termed as being incompatible. To date, experimenters such as Willingham and colleagues (2000) have manipulated S-R compatibility to investigate a range of effects. However, a particularly intriguing effect has been noted by Deroost and Soetens (2006) who have claimed that learning of an incompatible sequence can be greater to that of a spatially compatible variation. The authors argue that the effect that they notice in their experiment is not an effect of task difficulty, as an additional experiment seeking to address that issue failed to produce similar effects. It is difficult to fully understand the complex processing that has occurred in this experiment compared with others, as Deroost and Soetens (2006) employ a rather novel probabilistic sequence structure based on a 50% rule associated individually with each location. This means that with each location, the following position will always go to one of two (out of four) possible locations. However, a corresponding experiment investigating compatibility effects adapted the design to involve deterministic SOC sequences (Koch, 2007). Again it was discovered that the learning for incompatible response mappings were better than that of a compatible condition. Nevertheless, Koch (2007) has been far more cautious with his interpretation of results, claiming that a magnitude effect (based on far slower RTs in the incompatible condition) may be

consequently inflating learning scores in the incompatible condition due to much slower mean RTs compared to compatible responses.

Whatever the explanation, the understanding for why incompatible S-R mapping conditions can reveal superior learning is unclear. If one is to assume that task difficulty and/or magnitude effects are not the main reasons for this effect, it is difficult to justify an explanation that satisfies what we already know of sequence learning. A remaining possibility and one which may have even greater implications on the field regards the particular learning metric that is used in the vast majority of experiments. As mentioned, there are several reasons for why measuring learning through a random block towards the end of training is not ideal. As well as the potential magnitude effect proposed by Koch (2007), there may be a more significant behavioural effect that is being exploited by S-R incompatibility during random block performance. As this has not been directly tested, it is difficult to identify whether there is an association between the Deroost and Soeten's (2006) behavioural results and the way they have measured learning. However, it remains possible that introducing unexpected items may have an additional cost during a more difficult incompatible S-R mapping condition, which is independent to learning.

### **1.3. Task based learning**

One unifying view of learning based on different components is that participants are learning based on the specific paradigm that they are performing (Logan, Taylor, & Etherton, 1996). In some cases it has even been suggested that participants are able to inhibit information from competing perceptual resources in order to perform the primary task (Keele et al., 2003). This is certainly consistent with previous literature relating to dual and concurrent learning or that of learning in the presence of a distractor (see chapter 1). However, as discussed, this can be dependent on the degree to which something is distracting. Generally, it is believed that participants will form a representation of the information that is available (Keele et al., 2003). This information can be chunked based on the type of information presented, such as relational structures as well as spatial features (Koch & Hoffmann, 2000a). It is considered that under these task set processes, learning of multiple strands of information should only be possible if the secondary strand required similar processing or that the learning was processed in a similar way (Logan et al., 1996).

#### **1.3.1 Dual module learning system**

Keele and colleagues (2003) have proposed a dual based system of learning attempting to explain processing of sequence learning systems based on what they describe as different



dimensions. These authors attempt to explain that in this case, their use of the term dimension refers to the modalities that are present in learning (such as motor or perceptual) as well as the specific sub categories of these modalities (for example perceptual features can refer to colour or spatial cues independently). Under these parameters, Keele and colleagues (2003) propose that learning takes place under unidimensional or multidimensional modules and that the two can even interact.

The unidimensional system, it is argued, occurs in the absence of awareness and is therefore, an automatic process of learning, meaning that it is involved in exclusively incidental learning (Keele et al., 2003). Although it can include various different modules, it is limited to single dimensions of learning at any one time. This can nevertheless include sub-categories of that dimension. On the other hand, it allows individuals to perform two separate dimensions concurrently as long as they are not contributing to the same thing. For this reason, it is particularly useful in dual learning where sequential information is presented concurrently with task irrelevant tone counting. Therefore, it is not susceptible to distracting information from other dimensions as it is only focused on what is perceived to be the primary task as it can only use one dimension from the paradigm. In this case, unidimensional learning of multiple features may take place under contingencies where the system focuses on what is perceived to be the most important dimension (Abrahamse et al., 2010). Nevertheless, these contingencies must occur automatically (Abrahamse et al., 2010).

In contrast, the multidimensional system involves processing of within and cross dimensional modules concurrently, meaning that it can attend to both spatial and colour (perceptual features) as well as categorizing them with other dimensions (e.g. auditory tones) (Keele et al., 2003). However, this is only possible if the two dimensions are categorised with each other. Although it can also proceed incidentally, the focus of multiple dimensions is reliant on participants attending to information and, therefore, can result in awareness. Learning under this model can also be automatic as attention to information from multiple dimensions is suppressed in order to filter out the ones deemed to be irrelevant whilst attending to the meaningful information. This is achieved by identifying meaningful and predictive information from the sequence (Keele et al., 2003). However, if information is uncorrelated, based on the participants understanding of the task set, attention to these features can be suppressed and not processed by the multidimensional system. Learning is therefore possible in the presence of random secondary information, but only if it is not attended to, otherwise learning is disrupted. Keele and colleagues (2003) stress this is not necessarily because the distractor presents a cost or load on attention, but because it interferes with the categorization of this information. Due to its ability to comprise

information from different modalities, it is suggested that multidimensional learning is particularly useful for learning ambiguous sequences (Keele et al., 2003).

### **1.3.1.1 Evaluation of the dual model learning system**

Evidence for this dual system is presented by Curran and Keele (1993) using SRT task in which participants transferred from single task to dual task conditions during the course of training. Participants were divided into two groups (either informed of the sequence (explicit condition) or not (incidental condition)). Based on later awareness measures the incidental group were divided into high or low awareness groups. It was discovered that under single task conditions participants in the explicit conditions and high awareness incidental group demonstrated greater learning than the low awareness participants. However after transfer to dual task conditions (e.g. concurrently counting tones introduced between trials) participants in all conditions and groups showed a similar magnitude of learning. The authors argue that due to the formation of awareness, the single task sequence must have been performed under multidimensional processes. In this case, some participants were able to attend to certain features of the task which resulted in awareness whereas others were not able to develop this basis of awareness. However, the change in the magnitude of learning for the dual task learning suggests that a unidimensional system was developed to filter out the effect of irrelevant tones.

### **1.3.1.2 Revised stimulus to response based learning system**

However, a recently developed model claims that participants learn stimulus to response rules (see Schwarb & Schumacher, 2012). In this model, participants learn a combination of components that become consolidated in training. Therefore, participants' who are trained to perform a task in a certain way, for example with a spatially incompatible relationship between the stimulus and response keys, will develop specific S-R rules on which their performance becomes reliant so that changing the S-R rule to a compatible mapping may be lead to costs in sequence learning. Imaging studies of this phenomenon have even demonstrated that brain activity to sequenced and non-sequenced (random) trials induce similar activity when performed compatibly or incompatibly (Schwarb & Schumacher, 2009). The authors argue that this is evidence for neural activity reflecting S-R integration in performing a task regardless of whether learning is taking place or not.

Indeed Schwarb and Schumacher (2010) have argued the results of Willingham's (1999) compatibility experiment are a product of S-R rules. In the third experiment, of Willingham's (1999) study, participants who had learned a spatially incompatible SRT task

transferred to one of two compatible mapping tasks. Half of the participants performed a new visual sequence that engaged the same set of finger movements they had learned in the compatible task and the others performed the same visual sequence but consequently required a different set of finger movements. It was discovered that only participants who kept the same finger responses were able to continue to show learning. However, Schwarb and Schumacher (2010) claim the incompatible mapping was not different enough from the compatible to disrupt the S-R rules that had been formed before participants' transferred to compatible responses. Therefore, they replicated the study but produced a more complex incompatible mapping. In this case, they identified that with this more complex incompatible mapping, participants were not able to transfer learning. The only group that did show successful transfer was a third condition where participants performed compatibly throughout, maintaining the same S-R rule.

Schwarb and Schumacher (2012) believe that this S-R rule hypothesis can be used to explain many previous studies. They specifically mention Cohen and colleagues (1990) previously explained paradigm where participants successfully perform a sequence using three fingers before transferring to one finger responses. Schwarb and Schumacher (2012) argue that in this case the S-R rule is maintained but simply the mode of response is altered. Presumably this can also apply to cross effector designs where participants demonstrate continued learning when switching hands (Grafton, Hazeltine, & Ivry, 1998; Japikse, Negash, Howard, & Howard, 2003). Under these parameters they insist that learning would not be expected to be altered. The authors also draw from Willingham's (1999) observational sequence learning paradigm where learning is not present. Schwarb and Schumacher (2012) argue that this is once again compliant with their model as S-R rules are not able to form when responses are not made. Presumably, one can also provide an explanation to findings from Koch and Hoffman (2006), who identified, that participants cannot transfer learning from vocal to motor responses to the same sequence structure under the S-R rule hypothesis. In this case there is a very clear violation of S-R modalities that would surely be expected to result in a loss or at least attenuation of learning, as is report.

Another example of learning based on S-R rules is presented by Goedert and Willingham (2002) who assessed the effect of learning a primary sequence when the same participants are asked to perform a secondary sequence (either 5 min, 1 hour, 5 hours or 24 hours later). In all cases participants repeated the primary sequence 48 hours after their initial experiment. The authors discovered that regardless of the time interval between learning the primary and performing the secondary sequence, learning of the main sequence was impaired 48 hours later compared to a baseline group who had only learned the primary sequence. Learning of

the secondary sequence was also impaired in all cases due to proactive interference from the primary learning. This seems to extend the S-R rule learning hypothesis by implying that learning of task sets can distort learning of new information for up to 24 hours even if the task set is not altered. However, the consolidation of this original learning is also questioned by the findings that participants were unable to demonstrate learning when returning to the primary sequence (Goedert & Willingham, 2002). This is known as retroactive interference, where it has been shown that old information can become distorted by new material (Panzer & Shea, 2008). However, there are also cases where retroactive interference is not present (Panzer & Shea, 2008). It is difficult to assess how this corresponds with the S-R rule as changes to the sequence means that stimuli locations must also change. Nevertheless, it may be compatible with the task set learning hypothesis as the aim of the experiment is still the same in these studies, only the incidental sequence has changed. It does however, suggest that learning is more flexible than Goedert and Willingham (2002) suggest and that participants can learn two sequences in quick succession. Panzer and colleagues (2008) do not, however, investigate whether participants suffer from retroactive interference on their primary sequence.

### **1.3.2 Problems with S-R rule hypothesis**

The complexity of S-R associations have been further demonstrated in tasks where participants transfer to perform either, identical or a mirror image sequence when transferring hands (Deroost & Soetens, 2006a; Deroost, Zeeuws, & Soetens, 2006; Grafton, Hazeltine, & Ivry, 2002). Grafton et al., (2002) demonstrate that learning is maintained when the perceptual sequence is identical, or in a mirror image formation, when switching hands. In this case, all participants were trained with the non-dominant hand before transferring to the dominant effector. Deroost et al., (2006a) developed this finding by asking participants to instead perform with their dominant hand to begin with before either switching to their non-dominant hand or maintaining the same effector. In both cases participants transferred to a mirror image sequence or an identical one. The authors report that those who transferred to their non-dominant hand learnt the mirror and identical sequences equally well but those who did not change effectors did not learn the mirror sequence as well as the identical one. It is unclear how this would be reflective of the S-R model. Instead, these studies seem to demonstrate that the ability to learn is flexible and perhaps based on the strength of the task set learning. If this has been consolidated, learning of new sequences may be impaired. However, if it is not strong, learning of new sequences may not be distorted by proactive interference.

This raises the question of how long sequence learning is retained in memory. Willingham and Dumas (1997) have tested this using SRT over a one year period. They discovered that participants who performed an SRT task one year after their initial experiment performed the task faster than those performing it for a first time. Nevertheless, learning of the sequence was not different between the one year or novice group. These findings suggest that sequence learning is not present after a 12 month period and that RT improvements were due to task familiarity (Willingham & Dumas, 1997).

Furthermore, the S-R rule does not account for observational learning paradigms that have been mentioned previously that do demonstrate that participants are able to learn without forming these associations. One explanation may be that these rules and sensory modalities (based on visual or auditory stimuli or specific spatial or perceptual properties) can be compatible or interchangeable with each other. In the case of Koch and Hoffman (2006b) the changing of vocal to motor responses may not have facilitated a strong binding of multiple sensory modalities to allow transfer. However, certain observational to motor modalities may be able to facilitate this type of transfer. Indeed, Schwarb and Schumacher (2012) briefly allude to the contribution of eye movements in observational paradigms. It is possible that these eye movements need to be large enough in these cases to facilitate successful transfer to a motoric S-R rule. However, to the best of my knowledge there are no studies that have attempted to directly answer this question. Nevertheless, this may be an interesting direction to explore in sequence learning.

#### **1.4. Imaging studies**

In addition to research that has begun to unravel the very complex behavioural mechanisms behind sequence learning, there has also been important progress in understanding the neurological correlates of participants' performance. Building a general understanding of what goes on in the brain can not only reveal insights into the level and extent of processing required to perform these tasks but also the role of certain regions and how they interact with other centres during cognitive and motor performance, which may be especially important with regards to their impairment in clinical groups.

To date there are a great deal of experiments concerned with the learning of old (sequences that have been trained on) and new sequences during a combination of incidental and intentional paradigms. These range from tests using the SRT to experiments where participants are instructed to pull levers in a series of directions. Studies have consistently revealed activation in the frontal areas such as the DLPFC, pre-supplementary motor area [pre-SMA] and supplementary motor areas [SMA] (Hikosaka et al., 1998; Jueptner, Frith, et

al., 1997; Jueptner, Stephan, et al., 1997), as well as in some cases the basal ganglia (caudate, putamen and globus pallidus) (Jueptner & Weiller, 1998) for new sequences. On the other hand, trained sequences reveal activity in the putamen (Jueptner, Frith, et al., 1997) and SMA (Jenkins et al., 1994).

As mentioned, it is important to differentiate between sequence learning paradigms which recruit differing behavioural processes. Arguably, this is even more important during imaging studies, as subtle features of a task can implicate different processing areas. For example, motor learning tasks have revealed activity in the cerebellum (Jueptner & Weiller, 1998) in both new and old visual sequences, whereas the hippocampus (Jenkins et al., 1994) is active during tone sounding tasks.

A further important issue affecting activity patterns is the methodology of these experiments and the instructions that participants are given. For instance, Jueptner and colleagues (1997) have demonstrated prefrontal activation that begins to disappear during sequence consolidation, increases when participants are asked to attend to what they are doing. It is thought that this is due to a prefrontal loop between the DLPFC and striatum where learning of consolidated information is replaced by the putamen. Jueptner and colleagues (1997) results seem to indicate that once learning has taken place and the putamen is active, prefrontal processing can be once again increased by increasing load on attention. In this sense, participants may be reverting to a behavioural approach similar to when they begin the task.

#### **1.4.1 SRT imaging studies**

As well as prefrontal areas and the SMA, striatal activity seems to be of particular importance during incidental sequence learning (Aizenstein et al., 2004; Berns, Cohen, & Mintun, 1997; Destrebecqz et al., 2005; Doyon, Owen, Petrides, Sziklas, & Evans, 1996; Grafton, Hazeltine, & Ivry, 1995; Peigneux et al., 2000; Rauch et al., 1997; Rieckmann, Fischer, & Bäckman, 2010; Schendan, Searl, Melrose, & Stern, 2003). The striatum is comprised of the caudate and putamen, where the latter appears to be especially important in these tasks (Hazeltine, Grafton, & Ivry, 1997; Rauch et al., 1997). Although it has been suggested that the caudate interacts with prefrontal areas (Peigneux et al., 2000), this activity is usually correlated with weaker learners (Rauch et al., 1997) in incidental tasks or in those who are performing new sequences intentionally (Jueptner, Frith, et al., 1997; Jueptner, Stephan, et al., 1997). It has also been known to decrease in activity when switching from a well rehearsed incidental sequence (under tone counting constraints) to a separate (non tone counting) sequence (Grafton et al., 1995). Considering that Grafton and colleagues (1995)

did not associate the caudate with significant activity in the prior dual learning phase, its pronounced deactivation may nevertheless indicate that it has some role in later automatic stages but is only weakly correlated with this process. Although some studies have failed to find any processing in the striatum during sequence learning (Honda et al., 1998), it remains to be a largely consistently present region of activity in these tasks. Doyon and colleagues (1996) are amongst a host of researchers that have demonstrated the significance of the striatum (in this case the right ventral striatum) in the later stages of sequence learning as well as the cerebellum. They suggest that the role of the striatum in processing well rehearsed and consolidated sequence information is consistent with findings that participants with impairment in this area do not perform so well on these tasks. Conflicting evidence has however been presented by Berns and colleagues (1997) who have discovered increased activity in the right DLPFC in the later stages of two finite grammar sequences. The authors discovered that this activity decreases when a new grammar is presented, only to increase again towards the end of training. Conversely, they argue that the ventral striatum is responsive to novelty and activated in early stages of incidental grammar learning. They argue that the increased activity in the DLPFC may be the product of its role in sequence maintenance, made more necessary by their complex grammar. Therefore, the more participants trained the more they were learning and needing to maintain (Berns et al., 1997). The ventral striatum is on the other hand monitoring performance of these tasks and therefore, required in early stages when learning is developing (Berns et al., 1997).

An important underlying aspect of this activation concerns the degree to which participants may be aware of what is happening. Although the striatum is associated with later stages of performance and learning, the frontal and DLPFC (Honda et al., 1998; Schendan et al., 2003; Aizenstein et al., 2004; Destrebecqz et al., 2005; Schendan et al., 2003) are active in later stages of training (thought to be due to awareness). To isolate the particular significance of these findings, some studies have attempted to differentiate between activity associated with awareness and that which occurs in the absence of awareness. Aizenstein and colleagues (2004) devised an experiment in which participants responded to stimuli presented with different properties (shapes and colours) so both incidental and intentional properties could be presented. Participants were informed that the shapes would occur in a particular sequence but not the colours. Aizenstein and colleagues (2004) argue that prefrontal activity was present in response to both shapes and colour, implying that incidental processing may also rely on frontal areas. Furthermore, a study by Destrebecqz et al. (2005) attempted to explore implicit and explicit learning by manipulating response-to-stimulus intervals (RSI) to maximise one or other type of learning. They subsequently identified activity in the

prefrontal cortex during explicit learning whilst the striatum was involved when learning was dependent upon incidental processing. The authors also argued that the prefrontal cortex may interfere with the progression of implicit learning (Destrebecqz et al., 2005). These findings are consistent with reports of learning related activity in the striatum which only seems to occur after frontal deactivation. The absence of any such decline in activity may be preventing processing of incidentally acquired sequential information from developing into a systematically defined learning through habituation to the task. Whether frontal activity can occur definitively in the absence of any awareness and incidental learning is unclear (Rauch et al., 1997) but in the vast majority of cases the optimal pattern of activity and transition seems to entail early prefrontal/ DLPFC processing followed by striatal activity for consolidation. To this extent, Destrebecqz and colleagues (2005) may have a basis to support claims that explicit knowledge can impede incidental learning through the prevention of frontal deactivation. However, as explicit learning and new sequence learning are separate mechanisms, activity in the prefrontal cortex in this case may be more attributable to the possibility that explicit knowledge of a task engages neighbouring or even similar regions to when one is in the early stages of sequence performance. In support of this finding, Fletcher et al. (2005) have argued that incidental learning can be impaired by sustained activity in the lateral PFC (Fletcher et al., 2005). However, investigations of incidental and explicit learning have revealed conflicting accounts, regarding any interaction between frontal and striatal activity (Schendan et al., 2003; Willingham, Salidis, & Gabrieli, 2002).

Another aspect of sequence learning that can complicate the interpretation of results is the uncertainty regarding how much of the activity noticed is attributable to learning rather than simply motor performance. For example, event related fMRI scans have also revealed activity in motor areas when planning motor movements (Cunnington, Windischberger, Deecke, & Moser, 2003; Cunnington, Windischberger, & Moser, 2005). This is particularly important when considering the role of areas such as the SMA and basal ganglia which are critical to movement. However, these concerns have been alleviated by a particular study suggesting that in a sequence learning task activity is noticed in the motor cortex in early stages while this shifts to basal ganglia activity in later training when learning may be expected to be more pronounced (Seidler et al., 2005). Nevertheless, Seidler et al. (2005) admit that the use of a secondary feature may intrinsically alter the behavioural aspects of sequence learning, thus engaging additional processes.



## **1.5. Patient Studies**

Patient groups of particular interest to sequence learning are those with disorders or focal lesions involving the basal ganglia (such as Parkinson's disease (PD), Huntington's disease (HD) and dystonia), the cerebellum and fronto-striatal areas.

### **1.5.1. Effects of Basal ganglia impairment on sequence learning**

Patients with basal ganglia dysfunction have been repeatedly shown to be impaired at motor sequence learning using the SRT paradigm (Brown et al., 2003; Doyon et al., 1997; Jackson, Jackson, Harrison, Henderson, & Kennard, 1995; Kelly, Jahanshahi, & Dirnberger, 2004; Muslimovic, Post, Speelman, & Schmand, 2007; Shin & Ivry, 2003; Smith & McDowall, 2004; Smith & Mcdowall, 2011; Sommer, Grafman, Clark, & Hallett, 1999; Vakil, Kahan, Huberman, & Osimani, 2000; Werheid, Zysset, Muller, Reuter, & Yves von Cramon, 2003; Wilkinson & Jahanshahi, 2007). Primarily, the focus of interest has been on Parkinson's disease [PD]. Patients with PD are known to suffer from a depletion of dopamine producing receptors in the substantia nigra pars compacta (Yin & Knowlton, 2006). Due to this, motor functions become impaired, leading to involuntary movements that are synonymous with the disease. Based on the imaging evidence discussed earlier (see section 1.4.) it would be expected that this population should be impaired at sequence learning as the primary loci of damage resides within the basal ganglia and negatively impacts the striatum.

Due to the basal ganglia's role in motor movements, a further possibility during sequence learning is that participants are learning the specific S-R mapping of a task and simply becoming faster by virtue of improvements in task familiarity across training. Exner, Koschack, and Irle, (2002), argued that due to the basal ganglia's involvement in movement execution, it is possible that activity in this area as due to mastering motor movements involved in the task. In support for this, they found that in an SRT task, patients with focal basal ganglia lesions were slower at responding than controls, but their level of learning was nevertheless intact (Exner, Koschack, & Irle, 2002). Alternatively, Exner and colleagues (2002) argue that learning in the task is more accurately corresponded to the cerebellum and pre-SMA. This is inferred by a finding that participants with smaller regional volumes in these areas were correlated with weaker incidental learners. Furthermore, others have argued that although general impairments are discovered in patients with basal ganglia lesion, it does not lead to an abolition of learning (Vakil et al., 2000).

### 1.5.2 Evidence from Parkinson's disease

Support for the perspective that damage to the basal ganglia does not influence learning is also demonstrable in PD. (Helmuth, Mayr, & Daum, 2000; Kelly et al., 2004; Smith & McDowall, 2006; Smith, Siegert, Mcdowall, & Abernethy, 2001). Furthermore, some have argued that although PDs are found to be attenuated in comparison to healthy age matched controls, learning is nevertheless still present (e.g. Pascual-Leone et al., 1993; Wilkinson & Jahanshahi, 2007). A contributing factor to the performance of PD patients may be the specific methodology behind the sequence. For example, Kelly and colleagues (2004) report that PD patients can perform hybrid sequences (mixture of first and second order conditional structures) relatively well in an SRT task. A further defining feature to these studies may be due to differences in sample demographics such as age, stage of illness, medication state etc (Kelly et al., 2004; Smith et al., 2001). This is especially critical when performing *between group* comparisons of patients

Nevertheless, there are important implications to studies that show impaired learning in PD for our understanding of the striatum and its involvement in cognitive processing. Although research suggests that the frontal lobe is heavily associated with cognition, studies have demonstrated that the striatum may be more significant than once believed. Doyon and colleagues (1997), for example, demonstrated that participants with frontal lobe lesions outperformed PD patients in a sequence learning task conducted over a six week period. In this study, the experimenters trained all participants on four blocks of 100 trials, once every week. They report that PDs as well as patients with lesions to the cerebellum improved across the initial three week period but that learning seemed to plateau beyond that point. Patients with frontal lobe lesions, however, continued to improve throughout the entire six weeks of training. Consequently, Doyon and colleagues (1997) argued that the development and consolidation of sequence learning is reliant on the striatum and that participant's with PD were not able to proceed beyond the three week point as they were not able to enter into this later phase of learning due to striatal degeneration. This proposal is consistent with imaging data revealing activity in the striatum at later consolidation stages of sequence learning.

In addition to this study, many experiments have investigated the effect of medical interventions and the consequence that they may have on cognitive functions. One such study has focused on a group of PD patients who have undergone pallidotomy of the globus pallidus compared with another group who have not, as well as healthy aged matched controls (Brown et al., 2003). The authors discovered that PD patients who had not had

surgery were able to learn (albeit attenuated to controls) but that learning in the pallidotomy group was abolished. Brown et al. (2003) argue that patients in the surgery group are disadvantaged due to additional damage to the putamen, thus implicating it as a crucial element to the formulation of learning.

As well as structural deficits due to dopamine depletion, research has also investigated the effect of chemical imbalances in PD. As mentioned, patients suffer from dopamine depletion in the substantia nigra pars compacta, which in turn affects the rest of the basal ganglia circuitry through direct and indirect projections. In order to alleviate motor deficits, patients with PD are prescribed levodopa medication which (unlike dopamine) can cross the blood brain barrier and be converted into dopamine in the brain (Wade & Katzman, 1975). Nevertheless, it is believed that the effect of this medication, although largely positive for motor deficits, may impair cognition (Cools, 2006; Swainson et al., 2006). Gotham and colleagues (1988) first proposed the significance of what they called an “overdose” effect in PD based on levodopa medication creating too much dopamine in areas that do not require it. Kwak and colleagues (2010) have demonstrated this effect in PD patients tested on and off their medication in an intentional sequence learning task where patients were found to perform worse when taking levodopa (Kwak, Müller, Bohnen, Dayalu, & Seidler, 2010). This effect has been demonstrated in PD by a series of important investigations. For example, Argyelan et al. (2008) have demonstrated different activation patterns using PET, in patients with PD as a consequence to levodopa injections during a sequence learning task. They discovered that those who were not administered levodopa produced levels of learning related deactivation in the ventromedial prefrontal cortex during learning in a similar pattern to that of controls. They argue that levodopa medication interacts with this deactivation and may therefore interfere with the activation of learning related processing in other areas (Argyelan et al., 2008). This would again be consistent with imaging studies identifying activity in prefrontal areas prior to learning related deactivation. Furthermore, the authors note that this deactivation in the prefrontal areas were present in good learners.

Others have more directly associated the release of dopamine in the limbic striatum in relation to implicit sequence learning using PET scans. In fact Karabanov and colleagues (2010) have established that D2 receptor densities are specifically related to incidental sequence learning. The authors claim that this activity is reduced during tests of awareness such as the Process Dissociation Procedure (Karabanov et al., 2010) (see chapter 2, section 2.6). The authors argue that this is an indication of two separate processes involved between incidental and intentional, (awareness related) processing. It is perhaps surprising that dopamine release is noticed in the limbic striatum as this region is thought to be responsive

to reward based incentives. However, Karbanov and colleagues (2010) argue that the instructions they provide to perform as quickly and as accurately as possible may have been sufficient to engage goal directed behaviour imply correct responses to fulfil positive feedback. However, there are also connections between the limbic striatum and the corticostriatal loop (Yin & Knowlton, 2006), which have been argued to be involved with incidental sequence learning (Carbon et al., 2003). However, other studies using the SRT paradigm have demonstrated release of dopamine in the putamen and anterior parts of the caudate (Badgaiyan, Fischman, & Alpert, 2007). It is difficult to explain why there are such conflicting results but there remains a need to investigate the same effect in incidental sequence learning. Considering that the incidental SRT is thought to be more related to activation of the associative motor loop (Alexander & Crutcher, 1990; Alexander, DeLong, & Strick, 1986), which may be benefited by L-dopa medication due to its connections with sensorimotor areas, one may expect to see learning related improvements in this task.

### **1.5.3 Evidence from dystonia**

Another particularly relevant neurological disorder of interest is dystonia. Although there is evidence the disease causes structural problems in the frontal-striatal circuitry it does not present with the same degree of cognitive deficits that are seen in PD (Brown et al., 2003; Jahanshahi, Rowe, & Fuller, 2001). The limited research that exists in dystonia and sequence learning has thus far suggested that there seem to be relatively small if any impairments and that this may be due to neural plasticity, recruiting the cerebellum during these tasks as opposed to impairments in the basal ganglia and striatum (Carbon et al., 2003, 2011; Ghilardi et al., 2003). These findings support proposed frontal-striatal deficits in dystonia, as it explains recruitment of the cerebellum for processes that are otherwise performed in the striatum in healthy controls.

As well as Exner and colleagues (2002) investigations, other researchers have argued that the cerebellum is an important centre for sequence learning. Pascual-Leone (1993) and colleagues have for example demonstrated that PDs can outperform patients with cerebellar damage. The authors advance the arguments made by Exner and colleagues (2002) by suggesting that the basal ganglia is more directly involved in working memory processes. In contrast, they argue that the cerebellum is involved in the ordering of information and therefore, more appropriate for sequence learning.

#### **1.5.4 Evidence from Huntington's disease**

Due to the evidence supporting the contribution of the striatum, and in particular the putamen being activated in imaging studies, patients with Huntington's disease [HD] present further interesting implications to our understanding of the basal ganglia and its role in sequence learning. In this case, HD is primarily associated with impairments to the caudate (Bamford, Caine, Kido, Plassche, & Shoulson, 1989), supported by fMRI studies investigating sequence learning in HD that reveal attenuated activation in the caudate compared to controls (Kim et al., 2004). It has also been demonstrated that HD patients are impaired at incidental learning (Knopman & Nissen, 1991) and are consistently outperformed by healthy age matched controls (Knopman & Nissen, 1991; Willingham & Koroshetz, 1993).

Nevertheless, there are also studies to suggest that incidental sequence learning is not impaired in HD intentional learning is (Schneider et al., 2010). Consequently, it has been suggested that it is not the caudate which is responsible for these effects. For example, Brown and colleagues (2001) have reported that incidental learning of a sequence is intact in HD participants whereas intentional trial and error learning is impaired. These studies raise doubt regarding whether the caudate or at least damage to the caudate in HD is sufficient to alter incidental learning (Brown, Chacon, Lucas, & Channon, 2001).

#### **1.6. Animal studies**

In addition to imaging studies in human participants, animal literature can be used to extend and in some cases qualify our understanding of the likely neural mechanisms involved in sequence learning. For example, Hikosaka et al., (1998) have investigated the effect of reversible lesions in animal models (Hikosaka et al., 1998). This was achieved by directly injecting a GABA agonist into areas of a monkeys' brain (including the middle and posterior parts of the putamen and caudate). They discovered that injections in the middle and posterior putamen resulted in increased errors for old sequences but not new ones, whilst injections into the anterior striatum increased errors for new but not old ones. Results for the caudate were not significant.

Animal studies have also investigated sequence learning performance in mice infected with the DYT1 gene mutation for primary dystonia (Sharma et al., 2005). The authors report that although the mice had normal motor functions, their ability to learn new sequences was impaired. Support for the hypothesis for compensatory plasticity was also established by detection of increased activity in the cerebellum and well as left prefrontal cortex.

## 1.7. Computational Models

In order to better understand the contributions of different brain regions to learning it is helpful to consider computational models of their interaction. One proposal is that there are unique functional roles fulfilled by the basal ganglia and cerebellum in learning (Doya, 2000). The author argues that the basal ganglia are involved in reinforcement while the cerebellum is involved in supervised learning. Studies have already demonstrated that the basal ganglia can act as a reward based system, facilitating positive feedback on tasks with additional dopamine release (Frank, 2005). In addition to this the basal ganglia can also predict future rewards (W Schultz, Dayan, & Montague, 1997) which is implicated in the computational theory of reinforcement learning (Barto, 1995; Sutton & Gnoffo, 1998). Under this model it is believed that the basal ganglia and dopamine reward system will seek to maximise potential future reward by optimising sensory motor mappings. This can be facilitated by reducing error signals in order to reinforce performance (Doya, 2000). As a major input site of the basal ganglia, the striatum is thought to comprise of two compartments; the striosome, with its projections to the substantia nigra pars compacta (where dopamine is produced) and the matrix, which projects to output sites of the basal ganglia (substantia nigra pars reticulata and globus pallidus). It is believed that the matrix outputs will prepare for the highest expected future reward by reinforcing motor associations and systematically engage with the striosome (Doya, 2000). In other words, the basal ganglia will attempt to identify the primary selection system in order to minimise errors. Successful facilitation of this system should therefore result in the striosome initiating the release of dopamine in response to optimal performance. Such reward related activity has also been demonstrated in the areas of the cerebral cortex such as the DLPFC (Doya, 2000), suggesting that more specifically cognitive processes are taking place. Doya (2000) proposes that (i) cortical neurons retain more sensory input information than the striatum, (ii) striatal neurons show a greater range of activity based on the progression of a task than those in the cortex and (iii) dopamine neurones are engaged by unpredicted reward and sensory stimuli (Doya, 2000). It would therefore, appear as though the basal ganglia with its importance to the striatum and dopamine producing cells is actively focused on primary response selection facilitation, the successful application of which can result in reward based dopamine release. To speculate, one may consider activation in these areas of the basal ganglia and striatum during later stages of sequence learning to be indicative of participants (i) performing faster to a sequence and (ii) committing fewer errors; thus engaging these computational systems and maximising reward contingencies.

The cerebellum on the other hand monitors error based signals defined by Purkinje cell synapses (Kitazawa, Kimura, & Yin, 1998). Research has discovered that climbing fiber signals carrying error information innervate Purkinje cells resulting in bursts of activity called complex spikes (Davie, Clark, & Häusser, 2008; Knopman & Nissen, 1991). These complex spikes are thought to be a precursor for activity in the cerebellum (Doya, 2000). Kitazawa et al. (1998) have identified these complex spikes in signals they claim contain information about the end point error outcome once a movement is finalized (Doya, 2000). It would therefore appear as though the cerebellum is associated with proficiency of performance, supervising its accuracy through Purkinje cell inputs (Doya, 2000; Kitazawa et al., 1998). Furthermore, complex spike signals are also thought to be involved in the beginning of reach movements (Kitazawa et al., 1998). The authors claim that based on the active role of Purkinje cells and cerebellum, there is compelling evidence to suggest that it is heavily integrated with sequence learning and can be implicated in its improvement.

Together, these computational models have supported a theory that sequence learning may be dependent upon cortico-basal ganglia loops consisting of a prefrontal loop (including prefrontal cortex and caudate head) involved in early learning and a motor loop (including SMA and putamen body) which is engaged in later stages. In addition to this, computational models suggest that there are also cortico-cerebellar loops connecting frontal areas with Purkinje cells and the cerebellum. How these models can explain probabilistic incidental sequence learning is not so well defined. Imaging studies investigating the reaction of these areas in response to probabilistic sequences is needed to begin to address this issue.

### **1.8. General summary to introduction and aims**

There have been some fairly significant advances in our understanding of sequence learning in the past couple of decades. Studies have not only identified that learning can be dependent on specific behavioural aspects of the task but also the neural correlates of the processing. However, the extent to which this information is consistent for a novel paradigm such as probabilistic SRT is unclear. Many reports of slight inconsistencies amongst healthy controls as well as neurologically impaired populations may to some extent be dependent on the different methodological approaches taken. In the current thesis these issues will be investigated using a consistent probabilistic methodology with some variations in stimulus presentation and motor response patterns to examine the specific research questions.

### **1.8.1 Chapter 2 overview**

Here a more detailed description of the SRT to that already mentioned in section 1.1 will be provided. Furthermore, the general methodology to experiments conducted throughout this thesis will be explained as well as the equipment used.

### **1.8.2 Chapter 3 overview**

The first of a series of investigations will begin by attempting to clarify methodological dissociations in not only the presentation of sequences but also the learning metrics employed. In order to clarify previous results demonstrating greater levels of learning in incompatible response mappings, the same effect is explored for the first time using probabilistic SOC sequences. In a second study, a direct investigation of learning metrics as well as the impact of repeating stimuli is conducted to assess their contribution to learning. The aims of this chapter are to address the surprising findings of previous researchers and to develop the argument by introducing new concepts regarding how learning is measured and importance of considering variables that may be disproportionately represented (i.e. repeating stimuli) when comparing compatible and incompatible RTs.

### **1.8.3 Chapter 4 overview**

The literature review touches upon the concept of introducing extra information in order to improve learning. To explore this potential, the intention of this chapter is to identify whether additional information can positively modulate learning and if so, what specific features are useful in doing so. In addition to methodological questions, the issue of spatial and perceptual features of sequence performance remain largely unexplored in the wider field. It is important to address these parameters as perceptual features of the task may be central to the successful performance of SRT paradigms. Furthermore, research has identified that learning can be achieved under concurrent sequence as well as additional load settings but that the magnitude of learning is dependent on the additional parameters not exceeding a certain level of difficulty. However, the effect of additional information when simultaneously incorporated into the primary task is unknown in the probabilistic SRT task.

### **1.8.4 Chapter 5 overview**

Patient studies have further advanced our understanding of not just sequence learning but also how anatomical, structural and chemical processes can interact with different areas of the brain. In Chapter 5, for the first time the performance of the same group of patients is tested On and Off dopamine medication to directly investigate its impact on incidental



sequence learning. To this extent, there are several important questions that this thesis will attempt to address. Firstly, according to Gothem et al.'s (1988) overdose theory, it may be expected that participants with PD should be worse at performing the SRT when on their normal medication. However, evidence raised through the current thesis argues that due to the associative connections between the basal ganglia and frontal regions, and the evidence supporting dopamine release during sequence learning performance, participants with PD should perform better when on their medication.

### **1.8.5 Chapter 6 overview**

Furthermore, considering the great deal of sequence learning research in PD and HD, more needs to be known about dystonia and the unique cognitive implications it presents. As deep brain stimulation (DBS) becomes an increasingly common surgical intervention amongst movement disorders and other neurological illnesses, it is crucial to investigate its impact on cognitive resources in these patients. As studies have revealed variable results but there are some indications that stimulation of the STN can modulate learning, it is of interest to monitor the influence of GPi stimulation in dystonia. If it is the case that stimulation in the GPi can modulate basal ganglia circuitry and perhaps also its direct and indirect projections with the frontal lobe, one can expect to find attenuated post operative learning. However, if it is the case that patients with dystonia are adapting to use the cerebellum and not engage fronto-striatal networks, one may expect to identify no effect of surgery.

### **1.9. Summary**

The thesis aims to harness information from multiple fields of psychology based on behavioral and neuropsychological studies in order to answer some important questions but also to demonstrate the importance of having a general understanding for how the two can be crucial for one's interpretation of results. In doing so, the message of the thesis aims to demonstrate that there are many concepts in sequence learning that have still not been clearly defined and that the development of the literature would benefit from a merger of cognitive and neurological aspects of learning.

## **Chapter 2**

### **II. General methods section**

#### **2.1. Overview**

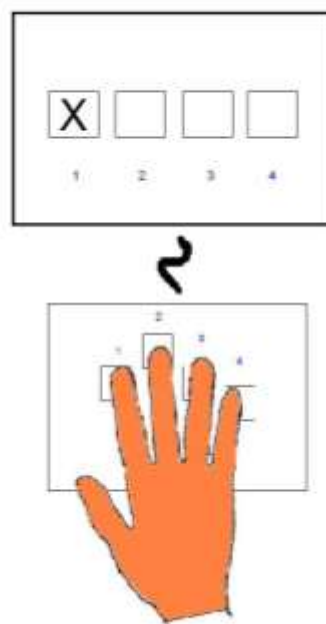
The following chapter will describe the common dimensions that are consistent across most, if not all, experiments in this thesis. In all studies the SRT task has been employed extensively to investigate a wide variety of features of incidental sequence learning (Cleeremans & McClelland, 1991; Jimenez & Mendez, 1999; Nissen & Bullemer, 1987; Shanks et al., 2003; Wilkinson & Shanks, 2004). In the original version of the SRT (Nissen & Bullemer, 1987), an array of four horizontal boxes appeared across the centre of a display monitor and participants responded to a target appearing within one of the boxes by pressing a spatially congruent button on the keyboard. The experimenters found RT became faster over time when a cycling 10-item repeating sequence of locations was presented compared to an entirely random sequence of locations. The principal features of this task have been replicated in many studies and will be maintained in the coming series of experiments.

#### **2.2. General specifications of the SRT tasks**

The thesis will introduce a number of novel innovations and adaptations to the classical SRT designs whilst still replicating important features from various previous researchers who have contributed to the development of the paradigm. In the majority of tasks, four boxes were presented horizontally across the centre of the monitor. In general, the stimuli were viewed from approximately 57cm, at which distance 1cm subtends approximately 1 degree of visual angle (so all sizes can be read as degrees or cm). The box dimensions were either 2.6cm high by 2.6cm wide or 4cm x 3cm with a spacing of 1.5cm between each. The current target stimulus was always denoted by an “X” symbol (1.7cm x 1.7cm), positioned in the centre of the box. Participants were instructed to respond as quickly as possible to the target location by using either a keyboard or button box (see figure 2.1) with four allocated response buttons. Consistent with most previous studies, participants were instructed to use the same finger for each button throughout training. However, whereas some studies have used multiple effector response priming (Jimenez & Mendez, 1999; Nissen & Bullemer, 1987; Willingham et al., 2000), experiments in this thesis will involve only responses from the dominant hand (index, middle, ring and little finger). This decision is based on the understanding that none of the upcoming studies are specifically interested with the consequence of multi effector transfer and many studies that have addressed issues such as compatibility and cognitive load have found single effector responses to be adequate.

Furthermore, patient groups involved in two of the coming chapters will involve movement disorder participants (Parkinson's disease and dystonia) where bimanual tasks may be problematic due to their conditions.

Following each response to the target stimuli, the symbol would move to its next location with a response stimulus interval (RSI) of either 250ms (normal participants) or 400ms (patients). The RSI refers to the time delay between the participants' last response and the presentation of the next target. During this interval, participants see four empty boxes before the next symbol appears. Nissen and Bullemer's (1987) original study contained an RSI of 500ms; however, subsequent studies have demonstrated that shorter periods are sufficient for learning to take place (Cleeremans & McClelland, 1991; Jimenez & Mendez, 1999; Wilkinson & Shanks, 2004) and that they may be better at limiting awareness (Destrebecqz & Cleeremans, 2001). However, most studies involving patient groups use higher RSIs in order to provide extra time between trials to prepare their next move (Wilkinson & Jahanshahi, 2007).



**Figure 2.1** Illustration of the button box used with an example of the stimuli seen on the monitor.

### 2.3. Construction of Stimulus Sequences

As discussed in chapter 1, the specific sequence structures used in past studies vary considerably in their length and properties. This makes it difficult to consider all sequence learning paradigms as a measure of similar cognitive processes, due to the possibility that

these specific structures may be influencing the type and/or difficulty of learning that takes place. In order to remedy these concerns, Reed and Johnson (1994) proposed a set of rules for standardisation of sequenced structures, which have been widely adopted and will be followed in the current thesis. They proposed that sequences should be constructed to adhere to a second order conditional (SOC) structure, which means the next trial location is uniquely determined by both the two previous locations (Reed & Johnson, 1994). In order to achieve this effect, Reed and Johnson (1994) structured their sequence to be twelve items long with four possible locations, each appearing three times in the sequence and all possible first order conditional (FOC) pairs present (i.e. location 1 can be followed by 2, 3 or 4 etc...). Crucially, the specific current transition is determined by the current location and the one before. This means that each 12 item sequence can be presented as a series of unique triplets, which describe all of the permissible sequence transitions (see table 2.1). As can be seen in table 2.1, each SOC sequence contains twelve unique triplet combinations. However, in some cases (SOC1 & SOC2 or SOC3 & SOC4); no one triplet is reproduced in either sequence. These are referred to as ‘parallel’ SOCs as their SOC properties are entirely different from each other whereas, for example, SOC1 and SOC3 share triplet combinations.

In all cases these sequences are consistent for their length (twelve items long), first order conditional frequencies (each location is preceded by each of the three possible alternatives), second order conditional frequencies (each item is predicted by its previous two occurring locations), location frequency (each of the four possible locations appears three times in the twelve item sequence), repetitions (no locations repeat immediately) and reversals (only one reversal occurs in each SOC sequence, e.g. 2-4-2 or 3-4-3) (Reed & Johnson, 1994; Wilkinson & Jahanshahi, 2007; Wilkinson & Shanks, 2004) (see table1). To date, many studies have used these SOC sequences in order to identify learning in their tasks (Koch, 2007; Rowland & Shanks, 2006a; Wilkinson & Shanks, 2004) as well as making their findings comparable with that of others. Many SOC sequences can be developed using this model but this thesis used four particular SOCs (see table 2.1) that have been used widely in the past (Koch, 2007; Shanks et al., 2003; Wilkinson & Jahanshahi, 2007; Wilkinson & Shanks, 2004).

**Table 2.1:** Triplets existing in each SOC.

SOC 1	SOC 2	SOC 3	SOC 4
242134123143	343124132142	121432413423	323412431421
SOC 1 triplets	SOC 2 triplets	SOC 3 triplets	SOC 4 triplets
242	343	121	323
421	431	214	234
213	312	143	341
134	124	432	412
341	241	324	124
412	413	241	243
123	132	413	431
231	321	134	314
314	214	342	142
143	142	423	421
432	423	231	213
324	234	312	132

### 2.3.1 Presentation of the Stimulus Sequence

Whilst SOC sequences introduced a systematic approach to measuring sequence learning there is also considerable variation in the way in which these sequences are presented. Traditionally, sequences were presented in a deterministic manner (i.e. the sequence is presented in fixed repeating cycles) but more recently, following Cleeremans and McClelland's (1991) finite grammar and more relevantly, Schvaneveldt and Gomez (1998), researchers have introduced probabilistic variability to the sequence presentation. The primary advantage of this method is that it makes the sequence structure less explicitly detectable, but it is also likely to constrain the representations which can be used as a basis for this learning (see chapter 3).

All of the studies in the current thesis are based upon the following probabilistic presentation, which is adapted from a design by Wilkinson and Shanks (2004). They were generally implemented using high probability primary (to be learned) and low probability secondary (not to be learnt) SOC sequences, where the presentation of each SOC is determined by probabilistic associations (Schvaneveldt & Gomez, 1998). For all but one experiment, a probability structure of 85%/15% likelihoods was adopted for primary and secondary sequences, respectively. This means that based on every transition (when the stimuli moves from one location to the next), there is an 85% chance that the next location

will be selected from the primary (probable) sequence and 15% likelihood that it will be taken from the secondary (improbable) SOC. To ensure there were no second order transitions in common between primary and secondary SOCs, the experiments in this thesis used pairs of parallel SOCs. Furthermore, the structure is regulated so that transitions from a probable to improbable location must at all times be consistent with SOC properties. This means that any change to an improbable trial must complete a triplet from the secondary SOC. As mentioned, of the 12 possible triplet combinations in each SOC, no one triplet is consistent between parallel SOCs but the first two locations occur once in each (e.g. 2-4-2 and 2-4-1 have the first two locations, 2-4 in common). In this case, a transition from the probable sequence from SOC1 after locations 2-4 is not randomly distributed but systematically associated to the only possible triplet completion from the improbable parallel SOC2 (2-4-1). This method provides a structured implementation of improbability whilst maintaining the rules for how locations transition from one to another. It is anticipated that as the improbable trials occur so infrequently, participants should only be able to anticipate probable triplet combinations. In the event of two consecutive improbable locations, the next item maintains this structure by continuing the selection process from the improbable parallel SOC (in this case SOC2, will result in the triplet 4-1-3). When returning to the probable SOC, the same rule is observed; where the next location will be a completion of a triplet from the probable sequence (1-3 occurs once in SOC1 meaning that the return will be to location 4 completing the triplet 1-3-4, see table 2.1).

One limitation to the original implementation of the design (Cleeremans & McClelland, 1991; Wilkinson & Shanks, 2004) is that, as trials are randomised across the whole stimulus sequence, there are likely to be blocks where improbable trials only occur on a few occasions. Indeed it is possible to have blocks where they do not occur at all. When the potentially low occurrence of improbable trials is coupled with the exclusion of error trials, it may result in a block with few to no data points to reliably measure learning. This can be a problematic feature if one wishes to monitor learning across blocks or at a specific time point in training. Although the reverse is also possible, a different approach was taken in order to maintain the regularity of these probabilistic properties for experiments where stages of learning were important, e.g. the compatibility (chapter 3) and secondary property studies (chapter 4). Therefore, transitions between probable and improbable items were fixed so that in each block there would be 85 probable and 15 improbable trials, e.g. randomisation occurred across blocks rather the whole learning phase. This modification helps to ensure that there are enough data points in each block to formulate a reliable comparison between RTs.

### **2.3.2 Estimation of Sequence Learning**

Learning of these probabilistic sequences is calculated through a subtraction of RTs for probable from those of improbable trials. This subtraction converts RTs into a calculated learning metric described as difference scores (Wilkinson & Jahanshahi, 2007), providing a simple measure of learning as potential allowing the investigator to identify differences in stages of learning. Evidence for learning beyond chance can be demonstrated by either a significant difference between probable and improbable trials and testing whether learning scores are significantly different from zero. This would indicate that participants have achieved an above chance level of separation between RTs for probable and improbable trials.

The specific approach that was taken to measuring learning in this thesis will vary across chapters based on the specific details of each particular experiment. In most cases, quite complex experimental principles of learning will be explored, requiring processing of secondary features such as S-R mapping and/or additional, informative load. It is anticipated that participants will take longer in these cases to establish learning, so in order to remove what may be particularly noisy data in the early stages of the task, the last four blocks of testing where learning in these more complex variables is being consolidated will be analysed. In isolating the most efficient period of training in this way, the risk of underestimating learning is minimised. Furthermore, it helps to maintain one of the primary benefits of the probabilistic SRT, which is that learning, can be measured through multiple blocks, reducing the likelihood that results can be influenced by participants performing particularly badly in any one block. Other experiments, however, will involve metrics taking all learning blocks into consideration. This is specifically true of patient work where previous studies using the same probabilistic SOC sequence have used all 15 blocks (Wilkinson & Jahanshahi, 2007) to measure learning. It has also been suggested that performance varies between early and late stages of learning in PD. As the patient studies are not concerned with stages of learning, it seems sensible to avoid this potential confound by taking all blocks into consideration like others have consistently done (Brown et al., 2003; Wilkinson & Jahanshahi, 2007; Wilkinson, Khan, & Jahanshahi, 2009).

### **2.4. Awareness measures**

In order to identify whether participants demonstrate any explicit knowledge of the sequence that they have been tested on, awareness measures were used after training. However, this remains a controversial aspect of sequence learning, with many studies that are consistently contradicting each other (Destrebecqz & Cleeremans, 2001; Destrebecqz et al., 2003; Jacoby, Toth, & Yonelinas, 1993; Jacoby, 1991; Shanks & St. John, 1994). A reason for this

may be that there remains a large degree of ambiguity regarding what is awareness, how is it displayed, whether it influences incidental learning and how can it be tested. Many researchers have chosen to test it through generation tasks (Jimenez & Mendez, 1999; Shanks & St. John, 1994), where participants are asked to replicate strands of the sequence. They are subsequently tested for whether they can replicate the whole sequence and, or the amount of triplets that they can produce. Nevertheless, it can be argued that this method does not distinguish between actual awareness of a sequence and motor priming which can be subject to motor incidental learning. Replication of a sequence or parts of it in this way may, therefore, be less of a representation of awareness than an extension of incidental learning under un-cued settings. In the current study two procedures were employed, which are outlined briefly below.

#### **2.4.1 Process Dissociation Procedure**

The Process Dissociation Procedure [PDP] (see Jacoby, 1991; Jacoby et al., 1993) is a technique where participants are not only cued for their capacity to complete segments of the primary SOC sequence on which they trained on but also to *inhibit responses*, which is extremely challenging when responding on the basis of motor priming. For the inclusion section, participants are presented with all twelve possible six item chunks of the sequence and asked to respond to the locations in the exact same way that they have done in the implicit section. After the five responses, four question marks appear in the four boxes and participants are asked to provide the sixth (final) location without any cues. The exclusion section differed only in that participants were instructed to provide an incorrect location, with the constraint that they were not to select the last presented location.

An estimate of explicit knowledge is calculated through an identification of whether participants are able to include more items from the primary SOC than from a baseline measure taken from included items completing a triplet from the parallel (improbable) version. If participants score significantly higher for the primary SOC, it would indicate that they have better control over completions of the probable sequence compared with the improbable. Scoring for the exclusion condition is calculated in the same way, however, explicit awareness is in this case considered to be present if participants are able to score significantly higher for completions from the improbable SOC than from the probable (primary SOC sequence).

As mentioned, a benefit of the PDP is that it measures awareness from more than one perspective and actively seeks to eliminate reliance on motor priming. However, a potential disadvantage of the design is that it is not usable by all sequence learning designs such as



Deroost and Soetens (2006) where no fixed sequence exists. Furthermore, under variations of the SRT, the same problems may occur, meaning that use of the PDP will be restricted to specific tasks throughout this thesis but not all.

#### **2.4.2 Recognition awareness**

The final explicit phase of testing involves gauging participant's recognition of the sequence. In this case, 24 six item chunks are presented to participants (who respond to each item in the same way as they have done throughout), who are instructed that half of the chunks will be part of the primary sequence that they have been training on and the other half will be new (participants are not informed that the new sequence items are taken from the improbable parallel SOC sequence). Once responses have been made for all six items, participants are asked whether they believe the chunk they have performed is part of the "Old" sequence that they have trained on or if it is a "New" pattern. Finally they are asked to provide a confidence rating based on whether their prediction of Old or New was either 1 = sure, 2 = fairly sure, or 3 = guess.

Scoring of this section is calculated through a combination of responses to Old vs. New and the three confidence outcomes. Therefore, participants were provided a score of, 1 = Old/Sure, 2 = Old/Fairly sure, 3 = Old/Guess, 4 = New/Guess, 5 = New/Fairly sure and 6 = New/Sure. Calculations are then divided into the appropriate sections so that the mean ratings for the Old sequence can be compared with mean ratings to the New. For participants to have been able to differentiate between Old and New sequences, one would expect to find low scores for the former and high scores for the latter out of a possible six. A significant difference between rating for Old and New sequence recognitions would indicate that participants are more inclined towards one than the other (also see, Jacoby et al., 1993; Wilkinson & Shanks, 2004).

#### **2.5. General procedure**

Participants were instructed that they were taking part in a reaction time experiment and the purpose of the study was to respond as quickly and accurately as possible to a series of targets that changed position on a screen. They were told the aim was to measure how rapidly they responded to items in these locations and how they maintained performance over an extended period. They performed (in most studies) 15, 100 trial blocks. In many studies, this was followed by a final section where they performed tasks designed to test explicit awareness of the sequence structure. Participants were encouraged to break as needed between blocks, and this was especially emphasised to the patient groups. In the

studies in chapter 3, participants responded using the keyboard (for comparability with two specifically relevant previous studies) but otherwise used an ergonomically designed response box. They were instructed to place four fingers from their dominant hand over the appropriate keys and to ensure that they used the same fingers to make the same responses throughout the experiment. Typically this involved a direct correspondence between the horizontal spatial position of the buttons and stimuli, but the S-R mapping was directly manipulated in two experiments. In all studies, participants performed a practice block (between 10-100 trials) until they were confident in the task. Following completion of the incidental learning phase of the experiments, participants were informed that they had been presented with a sequence of locations but that the length and order of the sequence was deliberately complex to hide its structure. In most instances, participants performed either one or two brief tasks to identify whether they had any awareness of the sequence. The tasks used were the process dissociation procedure (PDP; Jacoby, 1991; Jacoby et al., 1993) and a 6-item sequence recognition task. When performing both tasks, participants always performed the PDP before the recognition phase, but the order of the PDP was counterbalanced so half of participants performed the inclusion followed by the exclusion condition whilst the rest performed the reverse order. Responses were as within the incidental phase. Participants then performed the sequence recognition task where they responded to the stimuli in the same way and either indicated their recognitions by pressing the indicated response keys on the keyboard, or through selecting the response on the screen with a mouse. At the end of the experiment, participants were debriefed and an explanation of the study was provided.

## **2.6. Ethics**

Testing of all participants was subject to ethical approval obtained through Brunel University (for all student participants tested at Brunel University) in accordance with the Helsinki protocol as well as the National Hospital for Neurology and Neurosurgery (for all patients groups and age matched controls tested through the Institute of Neurology [IoN]). All participants were informed of their rights to refuse participation and to withdraw from testing at any time. They were also reassured that any information would be kept confidential. Consent from each participant was obtained prior to testing, after any remaining questions were answered. All participants were also debriefed after testing and informed of the purpose of the study.

## **2.7. Apparatus**

Testing was performed on a variety of desktop and laptop PCs; for each study the same machine was used. Responses for the experiment in chapter 3 were recorded using a keyboard, whilst the remaining experiments involved an eight button, response box (four for left hand and four for right, see figure 2.1).

## Chapter 3

### III. The effects of stimulus-response mapping compatibility on incidental sequence learning on a probabilistic serial reaction time task

#### 3.1. Introduction

Increased learning of the sequence is commonly quantified using indirect reaction time (RT) measures; either the increase in speed of RTs as testing progresses or the RT cost when unanticipated non-sequence items are presented. The latter is the most commonly used measure and calculated from the difference in mean reaction time between trials where items are selected from the learned sequence compared with the mean RT for random non-sequence trials. These non-sequence trials can be presented as either a large block of random locations once learning is well established or randomly throughout the experiment (which provides a continuous measure of the development of learning). Indirect measures have the advantage that they are not, in principle, contingent upon explicit sequence knowledge required for direct recall of the sequence, and so to some degree circumvent the controversy regarding the degree to which participants are aware of the sequence structure (Destrebecqz & Cleeremans, 2001; Shanks & St. John, 1994; Song et al., 2007; Willingham & Goedert-Eschmann, 1999).

Despite a vast body of research examining the SRT, there remains continuing debate regarding the basis of the learning represented by these indirect RT measures. Researchers have argued that sequence learning is dependent upon the perceptual properties of the stimuli (Cohen et al., 1990; Stadler, 1995; Willingham et al., 2000), the motoric responses (Bischoff-Grethe, Goedert, Willingham, & Grafton, 2004), the mapping between stimuli and responses (Deroost & Soetens, 2006b; Ziessler, 1994) or the relational structure between successive items within the sequence (Koch & Hoffmann, 2000a). A parsimonious interpretation of the diverse findings in the literature is that participants learn both sequences of perceptual stimulus properties and movements, but the dependence on specific properties may vary according to the parameters of the paradigm being used (Koch & Hoffmann, 2000b). For example, reliance upon learning groups of motor movements cannot explain participants' ability to learn probabilistically presented sequences. In such tasks there is always a degree of uncertainty as to the identity of the next item, which can only be resolved by attendance to the perceptual cue and as a consequence previous studies have reported that changes to perceptual features incur a RT cost (Grafton et al., 1998; Japikse et al., 2003; Willingham et al., 2000).

One way to investigate the nature of information which is used in different tasks is to compare the effects of manipulation of the stimulus-response (S-R) compatibility, e.g. the degree to which stimulus and response sets facilitate each other. In other words, the interest focuses on the degree to which learning differs in tasks where the configurations of the stimulus and response sets are mutually facilitatory compared with those where they are not. In an influential model, Kornblum and colleagues (1990) proposed, that compatibility effects can be explained by the activation of common dimensions shared by both stimulus and response sets. One commonly performed manipulation in SRT tasks is comparing learning for stimulus sets that share a dimension with the response set (e.g. the standard spatially configured SRT where 4 stimulus locations are mapped to 4 spatially congruent keys) with an SRT stimulus set that does not share this attribute overlap (e.g. 4 arbitrary symbols are mapped to 4 spatially configured keys). Such studies are contrasting the effects when stimuli and responses contain or do not contain a common spatial dimension. The general consensus of these studies is that whilst learning can occur on the basis of such non-compatible S-R set mappings, it is generally attenuated when compared to that for compatible response sets (Kornblum, Hasbroucq, & Osman, 1990). However, it has been argued that this effect may be specific to the spatial dimension (Koch & Hoffmann, 2000a).

Recently, two studies have reported markedly different effects when manipulating the strength of S-R compatibility within a stimulus dimension (Deroost & Soetens, 2006b; Koch, 2007). In these studies, the researchers compared learning between an SRT task with a standard spatial S-R mapping and an SRT task with a *spatially incompatible* S-R mapping (where the relative spatial location of the stimulus and the response are not in direct correspondence). Perhaps surprisingly, given the results for set level incompatibility, both studies found that increasing the complexity of the S-R mapping in this way led to a greater difference in RTs between sequence and non-sequence items in the incompatible compared with the compatible condition. However, interpreting the results was complicated by the consistently slower RTs in the incompatible mapping condition, and fundamental differences between the paradigms employed by Deroost and Soetens and by Koch, which were a probabilistic rule based task and a deterministically presented sequence, respectively. These researchers came to different conclusions regarding the meaning of their findings within their particular paradigms.

Deroost and Soetens (2006) argued that increasing S-R mapping complexity actually enhanced learning. Their conclusion was critically dependent upon the interpretation of a control condition in which increased RTs resulting from reducing the perceptual discriminability of the stimulus did not produce a similar increased separation between

sequence and non-sequence items. As a consequence, they concluded that the effect in the incompatible condition was not simply due to increased RTs due to task difficulty. Instead, they argued that sequence learning is enhanced when a more controlled selection of responses is required from a complex stimulus mapping as opposed to the automatic priming that occurs in compatible conditions.

In contrast, Koch's (2007) conclusion regarding the effect of the mapping manipulation in his experimental paradigm was that it reflected increased benefits of learning within the incompatible S-R mapping rather than enhanced learning per se. Koch further argued that this performance effect was mediated by the development of explicit sequence learning that resulted in the formation of "motor chunks", i.e. linked subsets of movements. Thus, in the learning blocks (as opposed to random blocks), improved RTs reflected increased reliance on groups of motor responses. These conclusions were critically dependent on the results of two tasks where S-R incompatibility was introduced via the Simon effect (i.e. participants responded according to the identity of the stimulus that appeared at non-behaviourally relevant location that could be spatially congruent or incongruent with the task).

However, one notable feature about these results (Deroost & Soetens, 2006b; Koch, 2007) is that effectively the same result (enhanced differences between sequence and random trials) occurs in two paradigms with apparently distinct features and processing demands. One possible resolution to this issue, as Koch (2007) notes, is that when directly manipulating the mapping complexity both his results and those of Deroost and Soetens (2006) could be equally explained by non-learning based performance costs, i.e. an interaction between the controlled selection of responses and response mapping complexity. For example, in both conditions when an unexpected event occurs, participants have to prepare to switch to an alternate response, and this switch could simply take longer to retrieve the correct response in the incompatible condition as it involves suppressing an automatic tendency to generate a spatially compatible response before selecting the correct response. Nonetheless, it also remains possible that the paradigms share features that are not initially apparent, which would allow the findings of both studies to be explained by the priming (or learning) of simple responses (or chunks). For Koch's (2007) deterministic presentation, this is obviously the repetition of identical motor chunks that forms the basis of his explanation of the affect. In contrast, as noted earlier, the use of a probabilistic presentation by Deroost and Soetens (2006) should have mitigated against a motor explanation. However, the probabilistic structure of their paradigm is unusual and enhanced performance may result from reliance upon the facilitation of a limited subset of motor responses, which is likely to interact with the effects of mapping compatibility.

The potential response bias in Deroost and Soetens (2006) paradigm results from the requirement to learn a probabilistic transition rule (i.e. each location is followed by one of two locations randomly selected with 50% likelihood) rather than a complex response sequence. The particular transition rule employed dictates that for two locations (1 and 3) the next item in the sequence can be a *return to the same location*, which may have resulted in a bias either from a simple priming of commonly repeated motor responses, the increased learning of sequence repeat responses or even priming of chunks of repeated locations. It has been previously established that repeated visits to a same location are especially salient, more easily learned and possibly more explicitly noticeable than transitions to non-repeated locations (Baddeley & Ecob, 1973; Bertelson, 1961; Grill-Spector, Henson, & Martin, 2006; Hyman, 1953; Kleinsorge, 1999). Therefore, these repeat locations are likely to be favoured, especially as a 50% rule will mean consistently choosing only one of the two possible locations will produce statistically optimal performance and that groups of repeats will exist. Furthermore, those two locations are also correct responses from the other two locations (2 and 4), so their increased salience might also create a response bias in those conditions as well. As a consequence, the magnitude of the effect reported by Deroost and Soetens (2006) is likely to be exaggerated by reducing the occurrence of two highly primed motor responses in the random block, especially if this interacts with non-learning based performance costs. Importantly, a facilitation of the rapid selection of motor responses is likely to lead to a relative favouring of incompatible mapping conditions where response selection is more demanding due to the need to suppress an automatically cued response.

Furthermore, the blocked measure of learning employed by Koch (2007) and Deroost and Soetens (2006) could have lead to an overestimation of learning in both studies due to the participant's awareness of a change in the stimulus set. In Koch's (2007) task, participants show a greater affect when they are explicitly aware of the current sequence and hence are more likely to be startled by the change in the structure following the transition to the random block. A similar effect is likely to also occur in the Deroost and Soetens (2006) task as, even if they are not explicitly aware of the rule structure, a reduced frequency in the *highly salient sequence repeats* may alert the participant to a change which might lead the participants to delay responses.

Therefore, the generality and processes underlying any effects of element level S-R compatibility mapping on incidental sequence learning remain to be fully clarified. The first experiment assesses whether learning is still enhanced for an incompatible condition when performance cannot be improved by simple motor chunking, a bias to repeated responses and any enhancement of S-R associations have to be based on representations in working

memory as well as immediate visual cues. The second experiment directly assesses the effects of location/response repetition and the specific learning metric employed.

### **3.2. Experiment 1**

In the first study, the effects of S-R compatibility measured in a SRT paradigm in which a second order conditional [SOC] sequence (i.e. the next location is identified by the previous two locations) is presented probabilistically with an 85% likelihood (i.e. 15% of trials are unpredicted breaks from the learning sequence) (Wilkinson & Jahanshahi, 2007; Wilkinson & Shanks, 2004). One advantage of this paradigm is it is unlikely that learning is based upon motor chunking (Koch, 2007) due to random occurrences of deviations from the response sequence and subsequent returns to the main sequence at a different point. Additionally, the SOC sequence contains all direct (first order) transitions from one location to the other three locations represented with equal frequency, but no directly repeating locations. Performance cannot benefit from simply priming frequently repeated motor responses or strengthening an association between the current visual stimulus and a single response, or limited subset of responses (Deroost and Soetens, 2006). For learning in the task to be based upon strengthening of S-R associations, it would require a representation of the stimulus that also includes the previous location/transition. In principle, if this were the case, it could still be facilitated in the non-compatible conditions via increased attention as Deroost and Soetens (2006) proposed within their paradigm.

Importantly, the inclusion of randomly occurring improbable trials during the whole sequence training period allows learning to be measured continuously, and not simply using a block in the late stages of training. This allows an assessment of the magnitude of the contribution of increased practice with an unfamiliar S-R mapping to sequence learning because RT decreases occurring in improbable trials are assumed to be largely attributable to increasing familiarity with the S-R mapping. This learning measure also avoids the potential alerting effect of a sudden switch to a block of random trials in with a large shift in response contingencies.

#### **3.2.1. Methods**

#### **3.2.2. Participants**

20 female and 2 male right-handed Brunel University psychology undergraduates (mean age 19.05, SD=1.05) participated for study participation credits. Consent procedures were in accordance with the Helsinki declaration and were approved by the Brunel Psychology



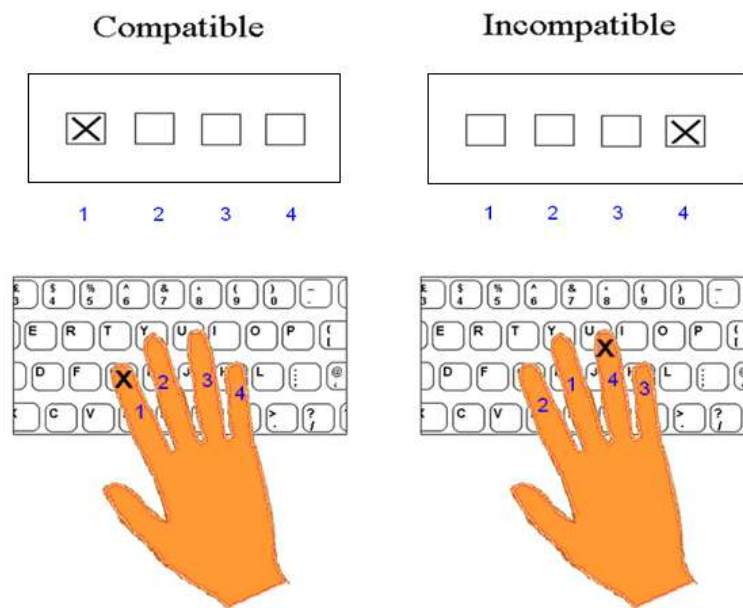
Department Ethics Committee.

### 3.2.3. Materials

All testing was performed on a Toshiba laptop (Satellite Pro A120) with a 15.1” widescreen TFT display and the keyboard was used for responding. The program was implemented in E-Prime version 1.1.

### 3.2.4. Design and Procedure

Participants performed a standard spatial SRT task in which each response was triggered by the appearance of a large cross ‘X’ (subtending 1.7cm X 1.7cm) in one of four boxes (4cm wide and 3cm high). The boxes were presented horizontally across the centre of the screen with a 1.5 cm separation. Participants were instructed to react to the stimuli as quickly as possible using the fingers on their dominant (right) hand to press four buttons on the keyboard, g, y, u and k (see figure 3.1). For each trial, the current location remained on the screen until the participant responded, with the next location being presented after a response stimulus interval [RSI] of 250ms.



**Figure 3.1.** Illustrating the S-R mapping for spatially compatible (left) and incompatible (right) conditions.

The stimuli were probabilistically presented 12-item SOC sequences (see chapter 2, section 2.3.). Four sequences, based upon the rules proposed by Reed and Johnson (1994), were used (see chapter 2, section 2.3.1). These were SOC1, SOC2, SOC3 and SOC4.

Participants were assigned randomly to either the compatible (N=11) or incompatible (N=11) S-R response mapping condition. In the compatible S-R mapping condition, the visual and response locations were spatially congruent, that is, 1-g, 2-y, 3-u and 4-k. The incompatible condition differed, only in the mapping of responses 1-y, 2-g, 3-k and 4-u (see Figure 3.1) Participants performed 100 random location practice trials to familiarise themselves with the S-R mapping before beginning the experiment. For each trial, accuracy of responses and RTs (in milliseconds) between presentation of the stimuli and initiation of a response were recorded.

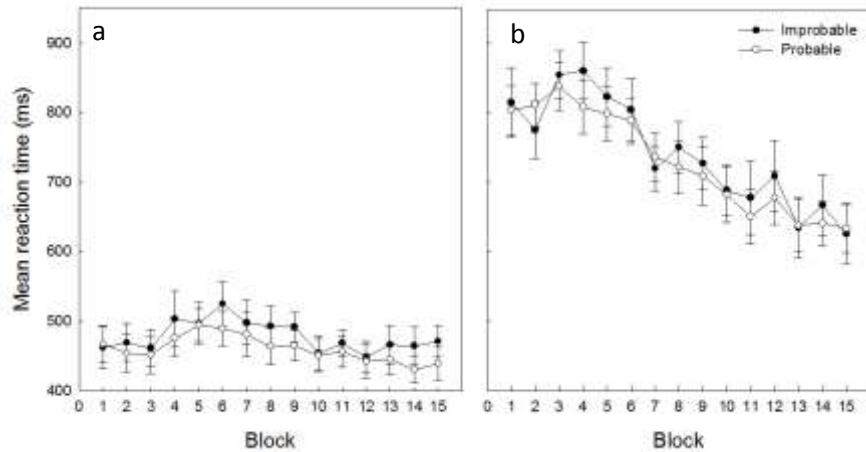
### 3.2.5. Data Analysis

All trials with erroneous responses, anticipatory responses (RTs under 100ms) and RTs over 1500ms were excluded. A measure of learning was derived by subtracting the mean probable from mean improbable RTs across the remaining trials. Learning was considered to have taken place if this difference score was positive and significantly differed from zero.

## 3.3. Results

### 3.3.1. Reaction Times

Figure 3.2 shows mean RTs for the probable and improbable trials across 15 blocks plotted separately for compatible (fig. 3.2a) and incompatible (fig. 3.2b) S-R mappings. These RTs were analysed using a 3-factor ANOVA with S-R mapping (compatible vs. incompatible) as a between participant factor and Probability (probable vs. improbable) and Block (1 – 15) as within participant factors. Greenhouse-Geisser corrections were applied where necessary. A significant main effect of Probability ( $F(1,20)=35.16, p<.001$ ) confirmed that probable trials were performed consistently faster than improbable trials, and hence learning had taken place within both S-R mappings. Additionally, a main effect of Block ( $F(5.05,101.06)=15.63, p<.001$ ) resulted from RTs becoming faster as testing progressed for both mappings and probabilities. The increased speed of RTs in the improbable condition (where sequence learning was unlikely) suggests that it was in part attributable to task practice effects. However, the change in RTs across blocks was much greater for the incompatible mapping compared to the compatible for *both* probable and improbable trials, which likely represents the important contribution of the continued consolidation of the complex S-R mapping (Mapping x Block:  $F(14,280)=9.21, p<.001$ ).



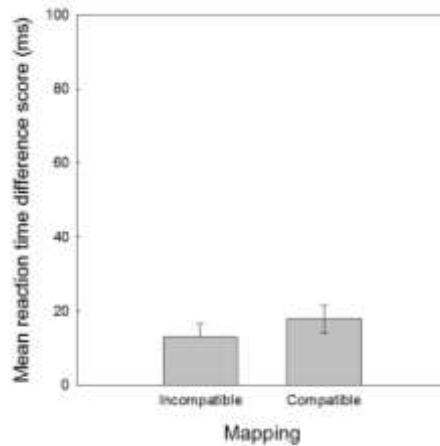
**Figure 3.2.** Mean RT in each for probable and improbable trials for both compatible (a) and incompatible (b) mapping conditions. Error bars represent 1 SE.

As can be clearly seen in figure 3.2, participants were consistently slower in the incompatible condition resulting in a significant main effect of Mapping ( $F(1,20)=42.94$ ,  $p<.001$ ). Critically, however, there was no indication of a difference in the magnitude of learning between the incompatible and compatible mappings (Mapping x Probability interaction:  $F(1,20)=.89$ ,  $p=.356$ ). Interestingly, there was also no significant change in the rate of learning (difference between probable and improbable trials) across training blocks (Probability x Block interaction:  $F(6.70,133.94)=1.00$ ,  $p=.433$ ). Importantly, there was no evidence for a mapping dependent difference in the rate of learning (Mapping x Probability x Block:  $F(14,280)=.877$ ,  $p=.585$ ), which indicates the absence any S-R mapping and learning interaction in this paradigm.

Figure 3.3 depicts the mean index of learning across all participants, which was calculated by subtracting their mean RTs for probable trials from those for improbable trials. The presence of learning was demonstrated by difference scores for both mappings being significantly greater than zero (compatible mapping:  $t(10)=4.842$ ,  $p<.001$ , incompatible mapping:  $t(10)=3.538$ ,  $p<.005$ ). Nonetheless, in contrast to the previous studies (Deroost & Soetens, 2006b; Koch, 2007) the magnitude of learning was actually lower for the incompatible compared with the compatible mapping, but this difference not significant ( $t(20)=.945$ ,  $p=.356$ ).

One explanation for the difference between the current and previous studies is that they measured learning late in training when it was well established whilst the current study measured learning throughout the whole of training period. The absence of any interactions between probability and block means that this is unlikely to have led to a significant underestimation of learning. Nonetheless, to be certain, a replication of the 3-factor ANOVA

analysis using only the final 5 blocks was performed. Importantly, as with the previous analysis, there was no significant interaction between Probability x Mapping ( $F(1,20)=.291$ ,  $p=.596$ ), again indicating no difference in learning for compatible and incompatible mappings. There were significant main effects of Probability ( $F(1,20)=9.211$ ,  $p=.007$ ) and Mapping ( $F(1,20)=21.703$ ,  $p<.001$ ) confirming that learning occurred during the final 5 blocks. Additionally, a significant main effect of mapping demonstrates that even by this stage RTs in the compatible condition were faster than for the incompatible condition (see figure 3.2). There was also still an interaction between Mapping x Block  $F(4,80)= 2.578$ ,  $p=.044$ ), which is probably due to the continued decline in RTs in both probable and improbable conditions for the incompatible mapping whilst RTs for the compatible mapping were similar across blocks. No other effects were significant.



**Figure 3.3.** Mean learning (RT difference between probable and improbable trials) for both compatible and incompatible stimulus mappings. Error bars represent 1 S.E.

### 3.3.2 Error Data

The mean percentage error rates for the compatible (3.96%,  $SD=2.26\%$ ) and incompatible conditions (5.13%,  $SD=2.77\%$ ) were, also analysed with a 3-factor ANOVA. None of the main effects or any interactions were significant, indicating that error rates were no different between S-R mappings.

### 3.4. Discussion

Sequence learning occurred within both compatible and incompatible S-R mapping conditions, but there was no evidence for a higher magnitude of learning attributable to the incompatible S-R mapping. Examination of the differences between mean RTs in probable (learning) and improbable (non-learning) trials revealed that the mean level of performance and rate of learning across blocks was of a very similar magnitude for both S-R mappings. If

anything this analysis might conceal a negative effect of the S-R incompatibility on sequence learning. In general, as previous studies have reported, RTs were significantly slower in incompatible mapping conditions, and so if the difference between probable and improbable RTs were in part proportional to their absolute magnitude, a larger difference would be expected in this condition. Additionally, the greater improvement in (i.e. faster) RTs in the incompatible condition occurred for both probable and improbable trials. Any improvement in RTs in the improbable trials is likely due to task practice and reinforcement of the stimulus mapping, which means that measures of learning based on RT improvement are likely confounded with these factors. Finally, an analysis of the pattern of error data revealed no differences between the two S-R mapping conditions indicating that increased task difficulty, evident from the slowed RTs, in the incompatible condition did not result in decreased accuracy.

The results are consistent with the proposal that motor factors (chunking or priming) may play a critical role in explaining previous reports of increased RTs in sequence learning for incompatible S-R mappings (Deroost & Soetens, 2006b; Koch, 2007). In the current paradigm, the utility of these motor cues was considerably reduced and so any effect upon which they are dependent would also be diminished. Specifically, the probabilistic presentation of the learning sequence meant it did not contain reliable repetition of identical “motor” chunks (due to repeated breaks in the sequence presentation at random intervals and rejoining at different points), which were present within Koch’s (2007) paradigm and form the basis of his interpretation. Additionally, the sequence contains every possible first order element transition and so is not susceptible to the simply priming of (or biasing towards) a very limited number of responses, which could potentially have occurred in Deroost and Soetens (2006) study. Importantly, if the results in that study were, as the authors propose, a consequence of the greater control required for response selection in the incompatible condition leading to a strengthening of S-R associations, then it might be expected to have occurred for the current paradigm. Though, the elimination of first order location transition cues (e.g. by including all possible transitions to different locations) may have lead to a different underlying basis for learning in the current paradigm. However, it is not possible based on the current study to assess the basis of Deroost and Soetens (2006) findings, and so this issue will be addressed in the next study.

The possibility that the results deviate from those of the previous studies because of other differences between the paradigms cannot be discounted, especially given the variation in the measurement of learning. Specifically, the current study employed a continuous measure of learning throughout the training period rather than examining the effects of learning in later

stages at the end of the experimental period as in the other two studies. Restricting the analysis of learning to the final five blocks had no effect on the overall result, which indicates that if the nature of the learning metric did affect the result it was not simply due to the timing of the measurement. However, it is difficult to determine whether these two methods for measuring learning produce different results as previous studies have employed only one of the measures and there are many other methodological differences between studies (e.g. deterministic vs. probabilistic presentation of sequence items).

Indeed, whilst there has been a large debate regarding the most appropriate ways to measure explicit sequence knowledge (and their sensitivity relative to indirect RT measures), there has been less interest in the affects of using different indirect methods for measuring learning (Haider, Eichler, & Lange, 2011; Jacoby et al., 1993; Jacoby, 1991; Jimenez, Mendez, & Cleeremans, 1996; Yonelinas & Jacoby, 1995). It has been generally assumed when comparing between studies using these different measures of learning that they are effectively measuring equivalent processes. However, Wilkinson and Jahanshahi (2007) noted there might be important differences in the fidelity of these two measures. More specifically, they claim that continuous measures of learning coupled with a probabilistic presentation of the learning sequence may give a more accurate measure than the more commonly employed blocked presentation. Critically, understanding the properties of different learning metrics is essential for interpreting the results of SRT studies and to help resolve this issue the next experiment compares the two measures acquired in the same paradigm.

### **3.5. Experiment 2**

The next experiment sought to clarify the basis of differences between the results of the first study and those published previously using a modified version of Deroost and Soetens' (2006) probabilistic rule learning task. Specifically, the first aim of the study was to assess whether there were differences between indirect measures of learning measured continuously throughout the experiment compared to those based on a single random block late in learning. The second aim was to assess whether the inclusion of repeated stimulus locations led to a strong response bias within those conditions.

In order to perform a continuous measure of learning, Deroost and Soetens' (2006) transition rule was modified. In the revised paradigm, transitions from any location were made to either one of the two locations used in the original study (80% probability) or one of the other two locations (20% probability). Hence, learning could be quantified, as in the first experiment, by comparing reaction times in probable and improbable conditions within each

block during the training period. Interestingly, the constraints imposed on the construction of the improbable condition (i.e. that they were the two location transitions not used in the original paradigm) meant that two repeat transition locations also occurred in these conditions. As a consequence, immediate motor facilitation effects of location repeats are subtracted when taking one RT from the other. The paradigm also included a block of random trials so that the two methods for estimating learning could be directly compared to see if they produce divergent results. Furthermore, location repeats were eliminated from the random block so that, by comparing RTs for improbable unlearned trials in the training blocks with RTs in the random block, it was possible to determine whether any apparent learning were due simply to the reduced probability of repeat locations. Crucially, the experiment enables an assessment of whether any differences in estimates of learning from the two metrics interact with S-R mapping compatibility.

As the new paradigm includes transitions with highly probable repeat visits to the same location, optimal performance can still be achieved by favouring these locations. However, by comparing RTs for location repeat transitions to those to a different location it is possible to quantify the magnitude of any bias and whether learning is driven by the favouring of such transitions. Additionally, evidence for chunking of repeat locations can be assessed by a speeding of response with the number of consecutive visits to the same location. Importantly, assessing the extent to which these factors interact with the response mapping may lead to a reinterpretation of the mechanisms underlying previous reports of enhanced learning.

### **3.6. Methods**

#### **3.6.1. Participants**

17 female and 3 male right-handed students (mean age 19.9, SD=2.2) from Brunel University took part in the experiment.

#### **3.6.2. Design and Procedure**

The experiment employed a probabilistic rule structure derived from the artificial grammar used by Deroost and Soetens (2006). In their experiment each location allowed transitions to two locations with a 50% probability. They used the following location transitions: 1 to 1 or 4, 2 to 1 or 4, 3 to 2 or 3 and 4 to 2 or 3. In the current paradigm, to introduce a continual measure of learning, the 50% rule was changed so that those location transitions occurred with 40% (probable) and for the remaining 20% of trials the location was selected randomly (50%) from the other two possibilities. Participants performed 16 blocks of 100 trials, with

the locations in the first 100 trials chosen entirely randomly so that participants could familiarise themselves with the task. One minor variation in the study was that random trials were presented in block 14 and not 13 as in the earlier study, and location repeats from the potential valid responses were eliminated.

A between groups design was used where participants were randomly assigned to either the compatible (N=10) or incompatible (N=10) S-R mapping conditions. In both tasks, stimuli presentation was identical to experiment 1. Participants were instructed to respond using buttons c, v, b and n. As within Deroost and Soetens' (2006) study participants in the incompatible condition responded according to a reversed S-R mapping (i.e. position 1 = N (right most letter), 2 = B, 3 = V and C = 4 (left most letter)). Stimuli remained on the screen until either a response was made or 3000ms time limit was reached at which point an error message was displayed for 750ms. The next location was presented after a response stimulus interval [RSI] of 500ms. These parameters were taken from Deroost and Soetens (2006).

### **3.6.3. Data Analysis:**

Trials with RTs over 1000ms were excluded as well as all trials with erroneous responses. In accordance with previous SRT studies, all anticipatory responses with RTs under 100ms were also excluded. Two measures of learning were derived for all error-free trials by subtracting the mean probable RTs from either (i) improbable RTs (ii) or from RTs of trials in the random block.

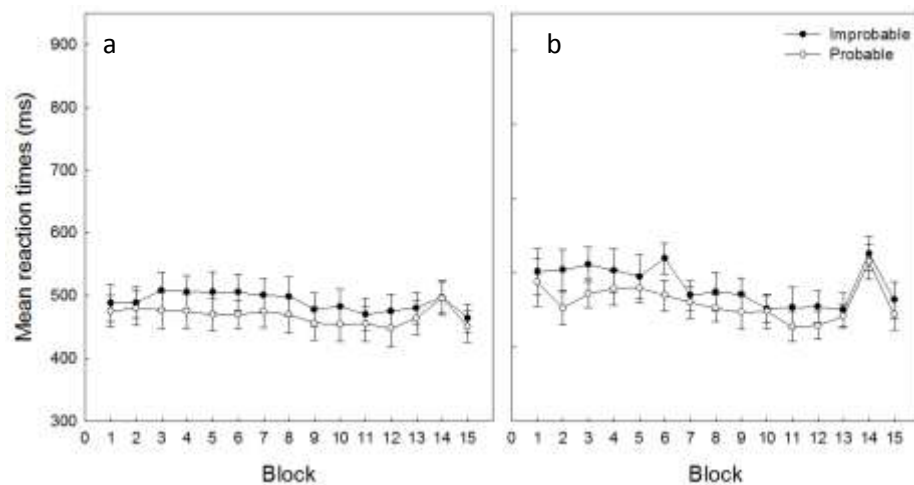
## **3.7. Results**

### **3.7.1. RT data**

Figure 3.4 plots mean RTs in each block for the compatible (fig. 3.4a) and incompatible (fig. 3.4b) S-R mappings. Separate means are plotted for probable and improbable trials excepting block 14 where all transitions were randomised and so this distinction did not exist. The experiment allows us to compare the effects of estimating learning through continuous measures with that from a late learning block. In order to assess the progression of learning (as within experiment 1), a 3 way ANOVA with Block (1-13) and Continuous Learning (probable and improbable) as within groups factors and Mapping as a between groups factor was performed. Learning took place across both mapping conditions (Continuous Learning:  $F(1,18)=56.831$ ,  $p<.001$ ) and RTs decreased consistently across blocks (Block:  $F(6.053,108.950)=6.865$ ,  $p<.001$ ) with the compatible condition producing faster responses (Mapping:  $F(1,18)=7.610$ ,  $p=.013$ ). However, no further effects reached significance. The



same effects were apparent if the analysis was restricted to the final five blocks (9-13) of the main learning phase. Consequently, as within experiment 1, this measure provided no evidence for a difference in learning between compatible and incompatible conditions.



**Figure 3.4.** Mean RT in each for probable and improbable trials as a function of both compatible (a) and incompatible (b) mapping conditions for blocks 1-13 and 15. Block 14 is entirely random and so there are no probable and improbable trials. Error bars represent 1 SE.

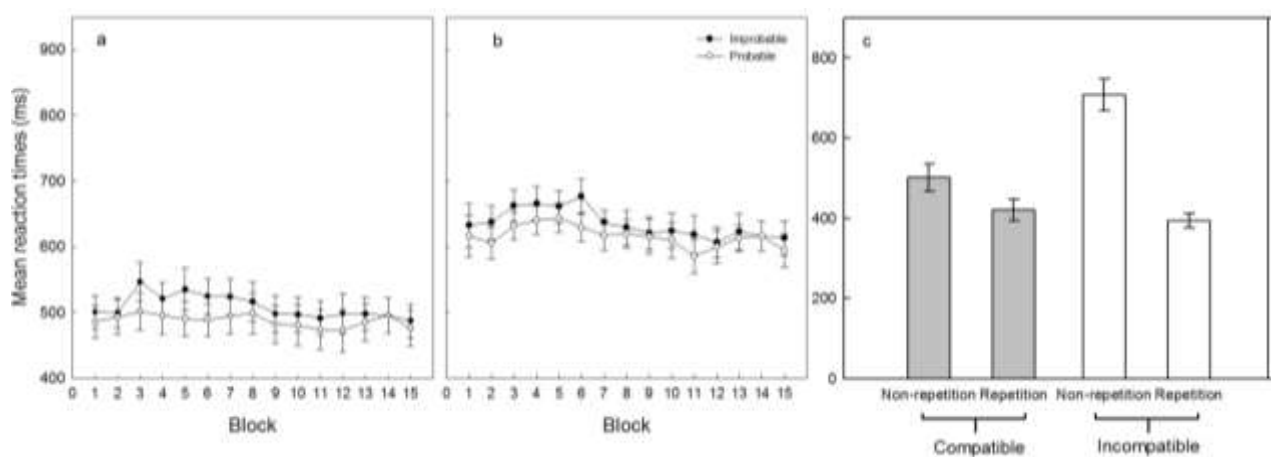
To assess learning on the basis of the late random block, a two-way mixed ANOVA was performed comparing the mean RT of probable trials in blocks 13 and 15 with the mean RT for block 14 (Blocked learning) as a within groups factor and Mapping Compatibility as between-groups factor. Learning was demonstrated by significantly slower RTs in the random block compared to sequence training blocks (Blocked learning:  $F(1,18)=70.722$ ,  $p<.001$ ). In general, RTs were slower in the incompatible condition (Mapping:  $F(1,18)=9.801$ ,  $p=.001$ ) and were especially slowed by the introduction of the random block (Blocked learning X Mapping:  $F(1,18)=6.956$ ,  $p=.017$ ). Therefore, in contrast to the measure of continuous learning, this metric apparently indicates that the incompatible response mapping leads to enhanced learning as reported by Deroost and Soetens (2006).

However, to validate the result, the analysis was repeated for the improbable trials (see fig. 3.4), which are not expected to be learned and so should show no RT difference when compared with the random block. However, the analysis revealed a slowing of RTs in the random block (“Blocked Learning”:  $F(1,18)=62.477$ ,  $p<.001$ ) that was especially pronounced in the incompatible condition (Blocked Learning X Mapping:  $F(1,18)=11.439$ ,  $p=.003$ ). There was also a main effect of stimulus mapping due to the generally slower RTs in the incompatible condition (Mapping:  $F(1,18)=9.727$ ,  $p=.006$ ). The results strongly suggest that increased RTs in the random block are driven by more than simply the effects of

sequence or rule learning. Importantly, the presence of stimulus location repeats in improbable trials but not the random block suggests they might contribute to the slower RTs.

### 3.7.2. Repeat analysis

To estimate the effects of repeat location transitions upon learning all RTs for such transitions were removed from the data and both ANOVAs testing for learning were repeated for the stripped data (see figures 3.5a and b). The results indicated an even larger RT difference between the mapping conditions for both the continuous ( $F(1,18)=14.21, p<.001$ ) and blocked learning measures ( $F(1,18)=12.36, p=.002$ ). However, estimates of learning were considerably lower and whilst this remained significant for the continuous learning measure ( $F(1,18)=35.92, p=.001$ ), there was only a trend towards significance for the blocked learning estimate ( $F(1,18)=3.98, p=.061$ ). Critically, there was no indication of an interaction between learning and mapping for either learning measure. Therefore, once repeat transitions have been removed, there was no evidence for enhanced learning in the incompatible response mapping condition.



**Figure 3.5.** Mean RT for just *non-repeat* probability probable and improbable trials as a function of mapping (compatible (a) and incompatible (b)) across all blocks. 3.5c shows the mean RT for repeat transitions and the RT for the initial transition to a location that potentially repeats in both both mapping conditions. Error bars represent 1 SE.

To further assess the impact of repeat transitions, a comparison was made between the mean RTs for the first transition to a location that could repeat (e.g. a transition from locations 2 or 4 to locations 1 or 3) and the mean RTs for a subsequent repeat transition from that location (see Figure 3.5c). The data was then analysed using a 4 factor ANOVA with transition type (Repeat vs. Non-Repeat), training stage (mean of blocks 1 and 2 vs. 12 and 13) and Probability as within-groups factor and Mapping Compatibility as between-groups factor. Participants were far faster at repeating a motor movement than initiating the movement for the first time (Transition type:  $F(1,18)=148.19, p<.001$ ) and this effect was especially

pronounced for the incompatible mapping (Transition type X Mapping:  $F(1,18)=61.25$ ,  $p<.001$ ). Figure 3.5c shows that the difference in RT between compatible and incompatible mapping conditions is largely abolished for repeat transitions. In general, as expected on the basis of learning, RTs were faster in the later stages of training (Training stage:  $F(1,18)=4.67$ ,  $p<.05$ ). Interestingly, there was a trend for a greater increase in RT speed for repeat transitions than non-repeats later in the experiment (Training stage X Transition type:  $F(1,18)=3.09$ ,  $p<.05$ ), which would be consistent with greater learning of repeat transitions. The only other significant result was the general effect of learning (Probability:  $F(1,18)=16.04$ ,  $p<.001$ ).

### **3.8. Discussion**

The current experiment investigated whether previous reports of apparent enhancements in sequence learning resulting from differences in S-R response mappings were influenced by the choice of learning metric and use of simple repetitions of the same motor movement. Learning was apparent for both spatially compatible and incompatible S-R mappings when comparing RTs for stimulus sequence trials to RTs for both randomly occurring non-stimulus trials (continuous learning measures) and a block of entirely random trial locations (blocked learning). Critically, the relationship between the magnitude and stimulus mapping compatibility was dependent upon the learning metric selected. On the basis of blocked learning measures, a greater magnitude of learning was apparent for the incompatible stimulus, which replicates and confirms the findings of Deroost and Soetens (2006). In contrast, however, the continuous learning measure revealed almost identical levels of learning between the two mapping conditions, indicating that the selection of learning metric was of crucial importance for estimates of the relative magnitude of learning.

The experiment also assessed the effects of using a rule which permits the repetition of the same stimulus location and as a consequence the same motor response. Participants were significantly faster when performing a repeated response to the current location than when initially transferring to that location. This effect was also larger for the stimulus incompatible condition, which likely reflects a reduction in the overhead for the more complex stimulus retrieval process. Importantly, excluding all location repeat trials and repeating the analysis of learning eliminated any differences in the magnitude of learning between the two mapping conditions. These results strongly suggest that repeat location visits increase estimates of learning based on comparing sequence RTs with a random block and this disproportionately affects the incompatible mapping condition.

### 3.9. General Discussion

Two experiments were conducted to examine the effects of S-R mapping compatibility upon motor sequence/rule learning. The first experiment assessed participants' ability to learn the structure of a probabilistically presented second order sequence whilst responding using either a spatially compatible or incompatible response mapping. Learning, measured by the RT difference between high frequency sequence trials and low frequency non-sequence trials, was found for both S-R mappings. In contrast to previous reports (Deroost & Soetens, 2006b; Koch, 2007) there was no evidence for any enhancement of learning in the incompatible mapping condition. However, the experiment sought to minimise reliance on motor cues (such as chunking) and so, the results would be predicted on the basis of Koch's (2007) interpretation of his results. In contrast, if learning is instantiated through a strengthening of S-R associations, then Deroost and Soetens' (2006) interpretation of their results that increased attention for the more demanding incompatible condition leads to a facilitation of S-R learning, might also be expected to apply in the current paradigm. However, the results are consistent with the proposal that a motoric response bias also underlies the Deroost and Soetens (2006) experiment. Nonetheless, in contrasting the results of the first experiment with earlier reports, an important potential confounding factor concerns the differences in the metrics used to measure learning.

The second experiment investigated the degree to which the magnitude of learning in the incompatible mapping condition might be affected by the choice of learning metric and the inclusion of repetitions of responses in the learned sequence/rule. This was achieved by using a novel variant of Deroost and Soetens' (2006) paradigm, which allowed measurement of learning by comparing RTs to learning sequence trials with RTs for either non-sequence trials occurring throughout the training period (as in experiment one) or from a block of random trials at the end of training. The continuous measure of learning produced almost identical estimates of learning for both mapping conditions. In contrast, estimates based upon the random block indicated a significantly higher magnitude of learning in the incompatible condition than the compatible condition. These results demonstrate the specific properties of the selected learning metric can interact with stimulus compatibility.

An analysis of the effects of stimulus repetition revealed that RTs were considerably faster when immediately repeating the previous response. This effect interacted with SR mapping complexity as generally slower RTs in the incompatible compared to compatible condition were not evident for repeated responses. However, a large element of this effect was attributable to simple motor priming as it was apparent in both the probable (sequence

training) trials and the relatively low-frequency improbable trials. Nonetheless, a trend for increased learning of repeat conditions suggests that this effect can contribute to overall estimates of learning. Furthermore, the magnitude of repeat location learning in the current study is likely to be less than in the original experiment where only two locations repeated during the training phase and did so with a higher frequency (e.g. 50% vs. 40%). Indeed a previous study has identified that RTs to trials containing 75% repeated stimuli are responded to faster than the remaining 25% random stimuli whereas another condition containing 75% alternating and 25% random trials are performed to with similar RTs as less time is required to prepare for a repetition (Bertelson, 1961). However, an important component of the subsequent increase in RTs in the random block is likely to be the elimination of the stimulus repeats, which did not occur in the original experiment. When repeat trials were eliminated from the analysis, estimates of learning were considerably reduced, and interactions with stimulus mapping were entirely eliminated.

Therefore, taking together the results of the current experiments and those reported previously clearly demonstrates that important variations in the estimates of learning occur based on the metric selected to quantify it. These differences do not simply affect the magnitude of learning, but potentially interact with other experimental manipulations like S-R mapping or design features (like the inclusion of stimulus repeats). Therefore, it is crucially important to consider the factors that might underlie differences between learning estimates based on comparing sequence RTs with RTs from random trials presented either in a block or distributed across the learning phase. One potential factor that could lead to lower estimates on the basis of the continuous measurement of learning is the influence of scores from the early practice stages of the task. Though, such an explanation would predict generally lower learning for continuous rather than blocked measures, but not the interaction with S-R mapping. Furthermore, when examining learning in the final 5 blocks, little difference was found in its magnitude from the overall estimate of learning across all 15 blocks.

One potentially important factor to be addressed in future studies is the role of awareness of stimulus structure and whether it interacts with changes to this structure. Specifically, if stimulus repeats are highly salient, then they could both trigger mechanisms of intentional learning and provide a strong signal to the change in the block structure when shifting to a random block (as location repeats disappear or change in frequency). The latter might be especially important in accounting for differences in the learning metrics as the continuous measures occur more discretely and so are unlikely to elicit deliberate strategy shifts. However, it is difficult to measure awareness when there is more than one equally likely

possibility at each location (Deroost & Soetens, 2006b) or every possible transition occurs at a particular location without higher order constraints (i.e. experiment 2). Nonetheless, some indication of the importance of this factor can be found in Koch's (2007) results which demonstrated that enhanced learning in incompatible conditions only occurred for individuals showing strong explicit knowledge of the sequence structure. Interestingly, it is worth noting that, although the numbers were small, Koch found twice as many participants (6 vs. 3) with significant explicit awareness of the sequence in the incompatible compared with the compatible S-R condition, which might indicate the increased attention to the stimulus (the explanatory basis of the account of Deroost and Soetens, 2006b) is more likely to result in awareness. Furthermore, results from previous studies indicate explicit sequence knowledge is less likely to develop in probabilistically presented SOC sequence, as employed in experiment 1, (Song et al., 2008; Wilkinson & Jahanshahi, 2007) than those with first order conditional sequences or deterministic presentations as used by Deroost and Soetens (2006b) and Koch (2007).

The issue of awareness may also have important implications for the relationship between learning of the sequence and the stimulus mapping. As participants are fully aware of the S-R mapping manipulation, they learn this in an intentional goal-directed manner. In contrast, if the participants are not informed of the presence of the sequence then at least initially learning is likely to occur incidentally (Cleeremans et al., 1998). These different forms of learning may recruit distinct neural mechanisms located in different brain areas (Destrebecqz et al., 2005; Poldrack & Packard, 2003; Poldrack et al., 2001). Poldrack et al. (2001) found that a probabilistic category learning task elicited neural activation in the basal ganglia and medial temporal lobe during implicit and explicit phases of the task respectively, and similar findings have also been reported for the SRT (Schendan et al., 2003). Although, other researchers have argued that participants use similar neural processing regions for incidental learning phases than intentional ones, it has been demonstrated that activity can vary based on whether participants are aware of a sequence or not (Willingham et al., 2002). The absence of any difference in the magnitude of sequence learning between S-R compatible and incompatible conditions when measured with difference scores in the current study is consistent with the proposal that the two learning processes occurred largely independently, which was further confirmed by the lack of interactions between the two forms of learning across the blocks. This is further supported by the presence of an interaction between awareness, SRT learning and response mapping reported by Koch (2007).

Taken as a whole, the results examining the effects of S-R compatibility are consistent with the proposal that there is no singular basis for learning within the SRT paradigms, and that

various (potentially interacting) systems of learning can be employed depending on the specific nature of task (Koch & Hoffmann, 2000a, 2000b). Some researchers have questioned this view and proposed more general rules, or critical stimulus dimensions, for the acquisition of sequential information. For example, Willingham and colleagues (1999; 2000) on the basis of a series of experiments examining the transfer of learning in that SRT task have claimed that its fundamental basis lies in learning response locations. However, it has been demonstrated on several occasions that sequence learning can be present under purely observational conditions where response locations and motor sequences are eliminated (Bird, Osman, Saggerson, & Heyes, 2005). This view of a multi processing system for S-R mapping and perceptual sequence structure has been supported by a recent imaging study (Schwarb & Schumacher, 2009). The authors demonstrate that neural activity to compatible and incompatible sequence learning conditions are similar as they both engage areas including the striatum and SMA but that there is also evidence for distinct processing in the DLPFC based on S-R compatibility and sequence learning. Therefore, it appears as though neural processing of learning based on S-R compatibility is to some extent different.

In conclusion, the results of the present two studies indicate that more complex stimulus response mappings do not necessarily lead to an enhancement in sequence learning that has been reported by earlier researchers. The existence of such enhancements seems to depend on the precise features of the stimuli, methodology and metric used to estimate learning. In particular, the results suggest that paradigms that facilitate learning of salient motoric responses or motor chunking may be more likely to produce this effect. However, participants' awareness that they are performing a learning task or that the stimulus presentation has changed may also play a critical role. The further investigation of such affects is an important future direction for research.

## Chapter 4

### **IV. Learning of complex additional information can be dependent on spatial and associative features during sequence learning.**

#### **4.1. Introduction**

Learning to perform basic cognitive and motor tasks in the real world frequently develops in incremental stages through the gradual reinforcement of repeated actions produced in response to the reoccurrence of the same situations. This gradual acquisition of habitual skilled behaviour has been termed procedural learning (Cohen & Squire, 1980) and is the subject of a very large body of research (Knowlton et al., 1996; Yin & Knowlton, 2006). One paradigm Nissen and Bullemer' (1987) Serial Reaction Time (SRT) task is a highly popular method for probing the learning of a series of responses to a structured a sequence of stimuli, which can occur even when participants are not made aware of the presence of that structure (i.e. are instructed it is a simple reaction time task) (Cleeremans & McClelland, 1991; Jimenez & Mendez, 1999; Nissen & Bullemer, 1987; Shanks & St. John, 1994). In this task, participants typically respond to each item in a series of stimuli appearing at predefined locations by pressing a spatially corresponding button, and learning can be inferred from changes in RTs (compared to a baseline of either earlier trials before learning has developed or random non-sequence trials). By introducing a large range of modifications to this apparently simple basic design researchers have attempted to probe the basis and limits of perceptuo-motor sequence learning (Jimenez & Mendez, 1999; Mayr, 1996; Willingham & Goedert-Eschmann, 1999; Willingham et al., 2000; Willingham, 1999). The general conclusion of these studies is that the occurrence of learning is robust in the presence of increased motor or perceptual demands, but the magnitude of this learning is highly dependent upon the specific task parameters (Rowland & Shanks, 2006a, 2006b; Shanks, Rowland, & Ranger, 2005). Nonetheless, fundamental questions (and controversy) still surround the information that forms the basis of learning within the SRT.

A common approach for examining the relative contribution of different components of the perceptual or motor features of the SRT to learning has been to introduce a cost, or to degrade, the specific variable of interest (Rowland & Shanks, 2006a; Schwarb & Schumacher, 2012; Willingham et al., 2000). If the manipulation attenuates learning then it is inferred that the variable contributes to learning (though interpretation is complicated by overall changes in RT resulting from the changes). Perhaps more controversially the absence of any effect has also been taken as indicating that the manipulated feature does not contribute to learning (Shanks et al., 2005). However, researchers do not always consider the



possibility that any changes to the ease with which a source of information can be used may lead the participant to exploit a different cue. Importantly, the precise methodology employed will often constrain the degree to which such a change is possible. This is a probable reason for the contradictory results reported across previous studies with regards to the relative importance of different variables used to learn the sequence (Koch & Hoffmann, 2000a; Koch, 2001; Schwarb & Schumacher, 2012).

A complementary approach, less frequently utilised, is to selectively enhance the available information to assess whether participants can use it to improve learning of the primary sequence (Jimenez & Mendez, 1999). In particular, it is possible to provide information that is not directly relevant to generating a response (which is determined by the horizontal spatial position of the stimulus), but nonetheless provides an additional constraint on the location of the next stimulus and so in principal if the two stimulus dimensions can be integrated it could facilitate sequence learning. Whilst this does not definitively establish that one stimulus feature is critical relative to another it can demonstrate that participants are capable of exploiting that information when it is available. The current experiments use this approach to examine the contributions of enhancing different non-behaviourally relevant aspects of the perceptual presentation of the stimuli and how this interacts with the perceptual properties required to make a response. In particular, the study addresses the role of spatial information and whether it is as proposed especially critical within sequence learning (Koch & Hoffmann, 2000a).

Although some previous studies have explored the importance of spatial features in sequence learning the findings have been mixed (Hartman, Knopman, & Nissen, 1989; Howard, Howard, & Mutter, 1992; Koch & Hoffmann, 2000a, 2000b; Mayr, 1996). Whilst some researchers have concluded that spatial information plays an especially important role in sequence learning other researchers have argued that other perceptual features are equally well learned. For example, Mayr (1996) examined a variant of the SRT where four different objects (each mapped onto different buttons) appear in four corners of a square display. The identity of the object was governed by a repeating eight item deterministic sequence, whilst the presentation location was determined by a distinct eight location deterministic sequence. RTs were considerably impaired in a block where either property was randomised, and most impaired by a disruption to both. They concluded that separate systems exist for learning each of these stimulus dimensions and were not dependent upon a motor response (as the finger movements were tied to the objects). Though, their conclusion is substantially weakened by the necessity for eye movements (and shifts in attention), which means an independent effector was producing a response to the spatial sequence and could therefore

explain the separate learning of both sequences. Indeed, a general concern with previous studies is their utilisation of paradigms with characteristics (e.g. deterministic sequence presentation) likely to emphasise motor response learning (Hoffmann, Sebal, & Stocker, 2001; Koch & Hoffmann, 2000a), which leaves open the generality of claims regarding the importance of spatial information for sequence learning. Furthermore, examining the effects of spatial compatibility between the stimulus and response introduces a problem in distinguishing the effects of a generalised rise in task difficulty and introduction of dual task demands with the specific change to the S-R mapping (Willingham & Goedert-Eschmann, 1999; Willingham et al., 2000; Willingham, 1999). The current study addresses these concerns in two main ways. First, by adopting a probabilistic presentation which cannot be simply completed by learning a fixed response sequence. Second, by manipulating a secondary perceptual dimension of the stimulus that does not affect the required response (which is based on the primary stimulus dimension) it is possible to introduce information that can potentially benefit the learning without altering the main task. However, in contrast to the majority of previous studies (e.g. Mayr, 1996) it does not seek to test the ability to separately process the secondary stimulus dimension to learn an additional implicit sequence, but whether the information is integrated with the primary stimulus dimension to enhance learning of a single stimulus sequence.

The introduction of secondary stimuli or additional dimensions to the primary stimulus in an SRT has been investigated previously by a number of researchers (Jimenez & Mendez, 1999; Rowland & Shanks, 2006a, 2006b; Schmidtke & Heuer, 1997; Shanks et al., 2005). The primary aims of these studies has been to examine whether there are costs of secondary tasks on incidental learning or to assess the possibility of concurrent learning of a multiple incidental sequences, which is typically motivated by a desire to determine whether attention is required for learning to occur in the SRT. In general, these studies have reported that it is possible to process secondary cues and potentially learn more than one sequence simultaneously, but there is divergent evidence with regards to the necessity of either explicitly directing participants' attention to the secondary cue or requiring them to perform a secondary task based on that cue. These differences partially reflect systematic differences between the stimuli and methodology employed across the different experiments. For example, Schmidtke and Heuer (1997) conducted a series of experiments in which participants performed an SRT task with each location selected from a repeating 6-item sequence and accompanied by a high or low tone (following an independent 5 or 6-item sequence). Different groups of participants performed the task under single task (respond to location only) or dual task (respond to location and high tone with a foot pedal) conditions.

They found that participants only learned the tone sequence when instructed to respond to it (dual task condition) and under those circumstances it also promoted SRT learning by disambiguating locations that repeated in the sequence. Jiménez and Méndez (1999) studied two groups of participants performing a SRT task in which 80% of the spatial locations were generated according to a finite state probabilistic grammar (in which every location could be preceded by one of two locations). The current location was indicated by a shape which also predicted the subsequent location with 80% likelihood, and so potentially disambiguating the position within the grammar. They discovered that participants only learned the relationship between shapes and locations if they performed a secondary task counting target shapes, but in contrast to Schmidtke and Heuer (1997) there was no benefit to primary sequence learning. However, evidence for passive learning of secondary cue has been reported by Rowland and Shanks (2006b) used a novel SRT in which two probabilistic horizontal sequences (each generated in a similar way to that employed in the current study) were presented simultaneously in separate rows. Participants were instructed to attend and respond to only the bottom row stimuli, but in subsequent testing showed some degree of learning of the sequence in the upper row (although less than for the primary sequence). Though, this learning was abolished when the perceptual load of the primary task was increased, which suggests that in part attention to the secondary property was required (Rowland & Shanks, 2006a, 2006b).

The proposed role for attention may explain differences with previous studies as the use of a behavioural response forces the participant to attend and process the cues relevant to that task. However, tasks may vary in the degree to which in passive conditions (i) there are sufficient attentional resources available to be automatically allocated to secondary cues, (ii) multiple dimensions are held simultaneously in working memory or (iii) the participant actively attempts to ignore these cues. These three factors are also partially driven by the processing demands of the secondary stimulus, which vary from task-to-task. In part the heterogeneous demands of various configurations of the SRT upon attention are also reflected in differences in reports regarding the effects of introducing a secondary task upon sequence learning. Whilst some researchers (Jimenez & Mendez, 1999; Schmidtke & Heuer, 1997) find little impact upon sequence learning when comparing dual and single task conditions other investigators (Shanks et al., 2005) have reported attenuation in performance. However, whilst these researchers have used different secondary stimulus features (e.g. tones and shapes) and largely employed a standard spatial SRT for the main task they have varied many other aspects of the paradigm, which makes comparisons across studies difficult. Therefore, a critical issue in understanding the differences between studies is to

systematically investigate the relationship between the perceptual dimension of the primary stimulus and those of the different secondary stimulus dimensions whilst as far as possible holding other critical aspects of the paradigm constant.

A further factor that may explain differences between tasks is the systematicity of relations between successive items in the SRT, which was termed by Koch and Hoffman (2000a; 200b) the sequence's relational structure. In SRT studies using deterministic sequences employing stimuli based on letters or digits learning was greatest when stimuli occurred in meaningful triplets in ascending (e.g. l, m, n or 1, 2, 3) or descending (n, m, l or 3, 2, 1) order (Hoffmann et al., 2001; Koch & Hoffmann, 2000b). Koch and Hoffman (2000b) interpreted these findings based upon priming of groups of responses, but it raises the question of whether the relational structure can also have an effect in paradigm that favours the perceptual rather than motor aspects of learning. A recent study by Jiménez, Méndez, Pasquali, Abrahamse and Verwey (2011) demonstrates the possibility of chunking of sub-components of a spatial sequence, and hence learning, can be facilitated by grouping items using a secondary perceptual cue (colour). However, Jiménez et al. (2011) employed deterministic sequence which leaves open the degree to which their effect is due simply to the facilitation of motor chunking or whether it extends into other aspects of SRT learning (Jiménez, Méndez, Pasquali, Abrahamse, & Verwey, 2011). Nonetheless, it remains possible that by clearly enhancing groups of stimuli it will promote learning of these groups, and that may have occurred in previous studies finding enhancing effects on sequence learning. However, it also remains uncertain how such chunking effects would be affected by probabilistic presentation, which introduces noise but also favours learning of perceptual regularities

In the current studies, participants' performed a series of SRT tasks using a probabilistically presented second order conditional sequence based upon Schvaneveldt and Gomez (1998). Importantly, the effects of introducing a secondary arbitrary perceptual (colour) or spatial cue (vertical location) are examined with primary task responses either based upon a perceptual (shape) or spatial (horizontal location) factors. Thus, the experiment s allows us to examine the effects when primary and secondary stimulus dimensions were aligned (e.g. Spatial-Spatial) or differed (e.g. Perceptual-Spatial). Importantly, effects are tested passively (e.g. participants were given no instructions regarding the secondary cue) based upon their effect upon on the learning of the main sequence. This is because if information from the secondary cues were integrated with the primary cue they uniquely specified the next location (e.g. transformed the task to a first order conditional) and so potentially remove the need to integrate the last two locations, which may make the task easier. Additionally,

arrangements of the secondary cue were varied so that they were presented in consecutive trials (to facilitate chunking of consecutive items), separated across the sequence (uniquely specifying the next location but not facilitating chunking) and randomly (to ascertain any benefits or costs simply from the presence of a cue). Finally, conditions were compared to see if they facilitated awareness. A change in learning strategy to a more deliberate intentional might promote awareness, but actually create a cost for sequence learning (which would presumably disappear with time).

#### **4.2. Experiment 1**

The first experiment examined whether the addition of a secondary colour cue to a spatial SRT task can modulate sequence learning. In the task the colour information was presented by systematically altering the colour of cross indicating the current location. So although not directly relevant to performing the task (responses are made to the spatial location of the cross) participants will need to attend to the stimulus, and it is assumed that the main task is likely to be of sufficiently low demand to allow a degree of attention to be allocated to process the colour. However, it is unknown whether any processing of the colour remains independent of that for the spatial aspects of the stimuli. In principal, if the two sources of information can be integrated then the identification of the next location can be performed on the basis of immediately available information and does not require knowledge of the last two locations (which might reduce the memory demands of the task).

The experiment contrasts two different ways of organising the colour cue with a monochrome baseline task. In the first colour condition the main 12-item SOC was organised into three successive 4-item colour groups. This means during the presentation of the stimuli the participant experiences a series of distinct colour chunks. The aim was to assess whether this facilitated grouping and hence learning based on these chunks compared to transitions across chunks. In the second colour condition, the colours were spread across the whole sequence to minimise consecutive occurrences of the same colour, which meant that the colour changed with all but one location transition in each sequence. This could potentially enhance performance by drawing attention more directly to the changes in colour, or be more demanding as it may make chunking of groups of items (which has to be done ignoring colour changes) more difficult. Nonetheless, it is critical to note that in both colour conditions each location transition is preceded by a unique colour and location combination, so if the cues can simply be integrated they are likely to both be better than the monochrome condition.

Finally, the experiment assessed whether the introduction of a secondary cue was more likely to lead awareness of the sequence structure than in monochrome conditions.

### **4.3. Methods**

#### **4.3.1. Participants**

30 Brunel University undergraduate, 23 female and 7 male, (mean age 20.2 SD=1.8) gave informed consent to participate in the study for course credits and were screened for colour blindness by self-report. All studies were approved by the Brunel University Psychology ethics committee.

#### **4.3.2. Stimuli and Materials**

In all experiments stimuli were displayed on a Toshiba Satellite Pro A120 laptop with a 15.1" WXGA TFT screen. Participants viewed 4 locations denoted by black outline squares (25mm by 21mm) on an even white background, which were evenly spaced (10mm) and horizontally aligned. The current location was denoted by the appearance of a cross, which was either coloured (red, green or blue). Responses in all experiments were made using an 8 button (4 for right hand and 4 for left hand) response box, ergonomically designed to suit left or right handed individuals (see figure 2.1, chapter 2).

For the SRT task, a 12 item second order conditional (SOC) sequence was used, where the current position is determined by the *previous two* locations. Sequences were created based upon the rules proposed by Reed and Johnson (1994) (see chapter 2, section 2.2). Sequences used were SOC1 and SOC2. Sequences were presented in a probabilistic manner, using a procedure adapted from Schvaneveldt and Gomez (1998) (see chapter 2, section 2.3.1).

By manipulating the colour of the cross indicating the current location the experiment allowed the introduction of a secondary cue incidental to the primary task (i.e. responding to the location). In colour conditions three colours (red, blue and green) were distributed across the SOC sequence so they occurred only once at each of the four possible locations (see table 4.1). Hence, the combination of colour and location unambiguously identified the next location. In addition to the standard baseline monochrome version of the SRT two colour conditions were created, blocked and mixed (see table 4.1). In the Blocked condition the three colours were presented in consecutive groups in the main sequence. Whilst in the mixed condition colours were distributed across the whole sequence to minimise the repeated occurrence of the same colour (i.e. only 1 immediate repeat of the same colour was permitted).

**Table 4.1.** Illustrates the distribution of the colour cue in each of the secondary cue conditions for SOC sequences (1 and 2).

	SOC1	SOC2
Colour Blocked	421341231432	431241321423
Colour Mixed	421341231432	431241321423
Monochrome	421341231432	431241321423

### 4.3.3. Design and Procedure

Using an independent group's design participants were randomly allocated to one of the three colour conditions (Blocked, Mixed or Monochrome). Participants were instructed to respond as quickly and accurately as possible when an x symbol appeared in one of the squares by pressing the spatially corresponding button with their dominant hand (see fig 2.1). For each trial, the current location remained on the screen until the participant responded. The next location was presented after a response stimulus interval [RSI] of 250ms. Participants were not told of the presence of a sequence or of the significance of the coloured items. The pairs of SOCs (1 & 2) and identity of probable and improbable SOC within the pairs were both counterbalanced across participants.

Participant performed a short practice trial to familiarise themselves with the task before beginning the experiment. The implicit task consisted of 15 blocks of 100 trials with a short break between each block. For comparability with later experiments primary analysis of learning was focused upon blocks 5-8, but analysis was performed on blocks 9-15 to ensure that different patterns between conditions had not emerged. In previous SRT tasks, participants have frequently been tested using just 6 blocks (Seger, 1997; Muslimovic et al., 2007), and so an accurate measure of learning should be attained across these blocks. The exclusion criteria were all error trials (15%) and all reaction times over 1000ms (4.7%), which were considered outliers caused by momentary lapses of concentration. In principal anticipatory responses (RTs below > 100ms) were also excluded but none were identified.

Two tests of sequence awareness, the Process Dissociation Procedure [PDP] (Jacoby et al., 1993; Jacoby, 1991) and sequence recognition test (Wilkinson & Jahanshahi, 2007; Wilkinson & Shanks, 2004), were employed to assess participants' ability to report the sequence structure. These tests were administered after incidental learning phase as the need to inform the participants about the nature of these tests would contaminate measures of

incidental learning. For both tests secondary cues were presented as they were during training phase of the experiment.

The PDP task consisted of two conditions requiring participants to not only complete (include) sequences but also inhibit (exclude) responses to the trained sequence, which avoids the possibility of completing the test based on simple motor priming. Participants performed 24 trials in which they typed a five item chunk taken from the original SOC sequence in response prompts on the screen (in the same form as the original SRT task). Question marks then appeared in all four boxes on the screen and participants were then required to either provide the next location in the sequence (inclusion condition) or respond with any location that was NOT the next item in the sequence (exclusion condition) (Jacoby et al., 1993; Jacoby, 1991). The conditions were performed in blocks that were counterbalanced across participants.

Participants received two scores for each condition, which were based upon a system presented by Jacoby and colleagues (1993) and developed by (Shanks et al., 2003). The first (termed the “old” sequence score) was the total number of sequences which were completed with the appropriate location from the trained sequence. The second (termed the “new” sequence score) was the total number of sequences completed with the corresponding location from the improbable sequence. If participants possess no awareness of the sequence then the old and new scores should be approximately equal. However, if they are aware of the structure there should be a significant difference between them, but in opposite directions for the inclusion and exclusion conditions (reflecting the differing task objectives).

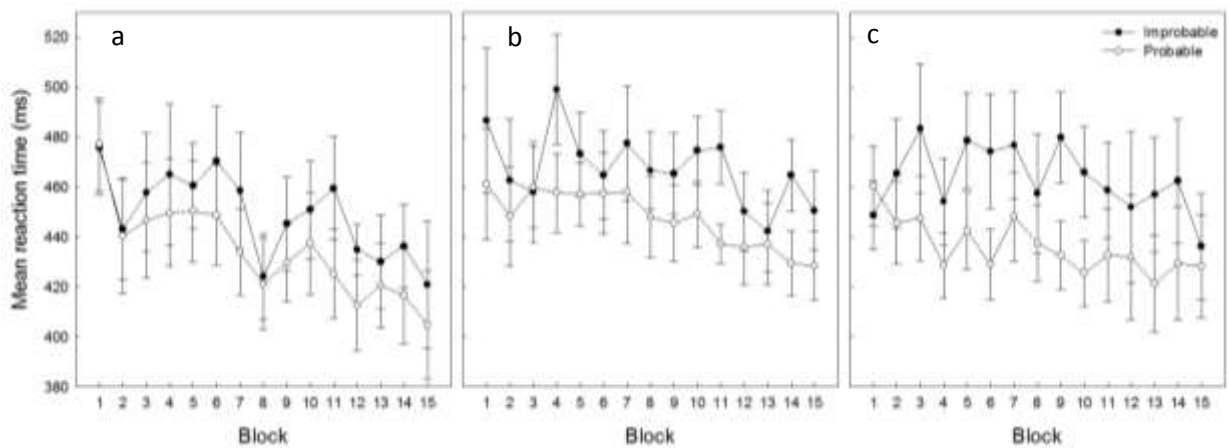
In the recognition task participants performed twenty four trials in which they typed six item sequences and then responded whether they believed it to be an “old” (part of the probable sequence) or “new” (taken from improbable sequence), as well as declaring the confidence in their own assertions (on a scale of 1-sure, 2-fairly sure and 3-guess). All sequences were different with fifty percent selected from the original probable SOC and the rest taken from the improbable SOC.

#### **4.4. Results**

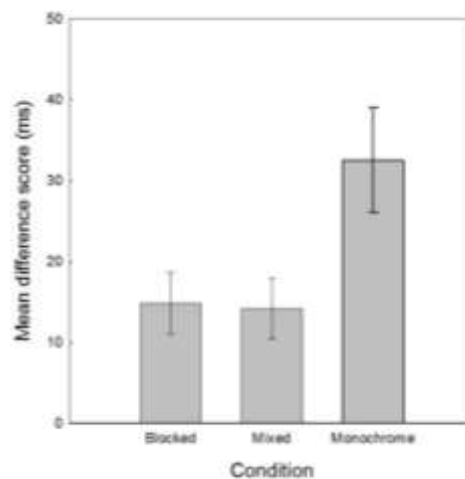
Figure 4.1 depicts the mean RTs in each block for the blocked colour (fig. 4.1a), mixed colour (fig. 4.1b) and monochrome (fig. 4.1c) conditions. A 3 way ANOVA was performed using mean RTs with Probability (probable vs. improbable) and Block (Blocks 5-8) as within group factors and Colour Condition (Blocked, Mixed and Monochrome) as between group factors. Sequence learning took place irrespective of colour condition (Probability:



$F(1,27)=54.768, p<.001$ ) participants became faster over the course of training (Block:  $F(1,3)=2.754, p<.048$ ). Furthermore, the magnitude of learning differed across the three colour conditions (Probability x Colour Condition:  $F(1,27)=4.208, p<.026$ ). To assess this effect for each of the three conditions the mean learning score (improbable minus probable RTs) across all four blocks was calculated and independent t-tests were used to compare the conditions (see fig 4.2). These indicated learning in the monochrome condition was higher than both the Blocked ( $t(18)=-2.347, p=.016$ ) and Mixed ( $t(18)=-2.449, p=.013$ ) conditions as is apparent in figure 4.2. The two chromatic colour conditions did not significantly differ. Furthermore, t-tests on different scores for all three conditions separately, confirmed that learning was significantly different from zero ( $p<.05$ ). No other effects were significant or showed a trend.



**Figure 4.1.** Mean RTs broken down by block and probability for Blocked colour (a), Mixed colour (b) and Monochrome (c) conditions. Error bars represent 1 SE.

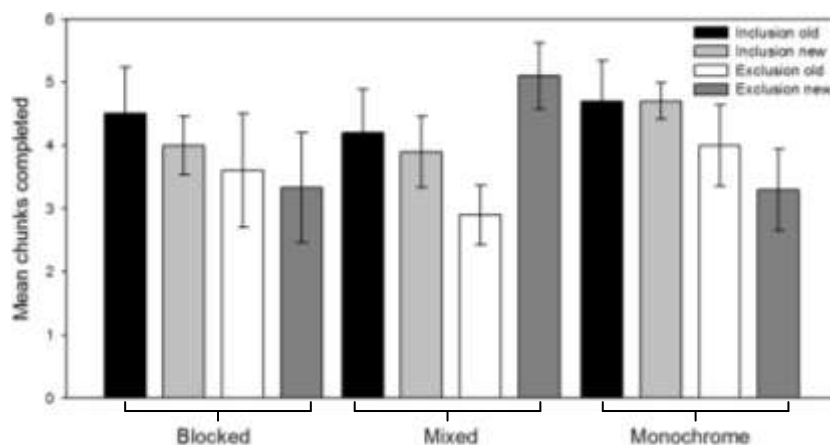


**Figure 4.2.** Mean learning (improbable-probable RTs) across blocks 5-8 for Blocked colour, Mixed colour and Monochrome conditions. Error bars represent 1 SE.

In order to assess whether the blocked colour condition promoted chunking of items in memory additional post-hoc analysis was performed on the RTs in this condition. The mean

RT was calculated for all instances when a third successive item in the sequence had been presented in the same colour (e.g. an item which was part of a colour chunk in the main sequence). This was compared to the mean RT for all items where the colour of successive items was different (e.g. when crossing colour chunks). This data was analysed using a 2-way ANOVA with Transition Type (within vs. across colour chunk) and block (5-8) as within participant factors. Neither the main effects nor their interactions were significant or showed a trend towards significance.

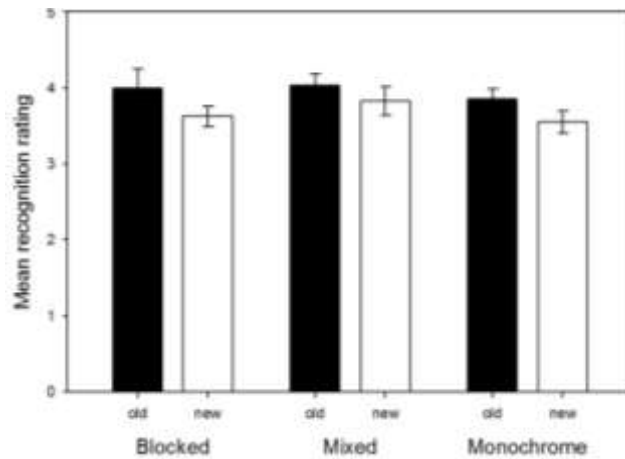
The PDP scores were analysed to identify whether participants could reproduce items from the trained sequence and could manipulate their knowledge of the sequence sufficiently to inhibit response based on the trained sequence. A 3 way ANOVA was performed with Task (Inclusion vs. Exclusion) and Sequence type (Old vs. New) as a within groups factor and Colour Condition (Blocked vs. Mixed vs. Monochrome) as a between groups factors. The main effect of Task ( $F(1,27)=5.240, p=.030$ ) indicated that scores were generally slightly higher for the inclusion (4.3) than the exclusion (3.7) tasks condition (fig. 4.3). However, the main effect of Sequence Type was not significant ( $F(1,27)=.061, p=.806$ ) nor was the interaction between Task x Sequence type ( $F(2,27)=1.135, p=.336$ ) indicating that participants did not produce more completions of the “old” (probable sequence) than the “new” (improbable sequence) and that this was true of all three conditions (See fig. 4.3). No other effects were significant.



**Figure 4.3.** Mean inclusion and exclusion scores for Old or New sequence in each colour condition. Error bars represent 1 SE.

Finally, awareness identity and associated confidence ratings were pooled into a single six-point scale using the following classification criteria 1= Sure new, 2= Fairly sure new, 3= Guess new, 4= Guess old, 5= Fairly sure old and 6= Sure old. A 2-way ANOVA with Sequence type (Old vs. New) as a within groups factor and Colour Condition (Blocked vs. Mixed vs. Monochrome) as the between groups factor. In general scores were higher for old

sequences than new ones (Sequence type:  $F(1,27)=5.217, p=.030$ ) (See fig. 4.4). However, the scores were very similar across colour conditions (Colour Condition:  $F(1,27)=.253, p=.392$ ) respectively. There was no evidence for any variations in the magnitude of scores for old and new sequences between the different viewing conditions (Colour Condition X Sequence type:  $p>.1$ ).



**Figure 4.4.** Mean recognition scores for Old and New sequences for all three Colour conditions. Error bars represent 1 SE.

Further analysis was conducted to identify whether the mean ratings in each condition for Old and New chunks individually were significantly different from chance level (3.5). In all three conditions scores were significantly different from chance level for Old chunks in the Blocked ( $t(9)=2.418, p=.029$ ), Mixed ( $t(9)=3.852, p=.002$ ) and Monochrome ( $t(9)=2.828, p=.010$ ) conditions (see fig 4.4). However, scores for New chunks were not significantly different from chance for the Blocked ( $t(9)=1.103, p=.150$ ) and Monochrome ( $t(9)=.351, p=.367$ ) conditions while there was a trend towards significance in the Mixed ( $t(9)=1.557, p=.077$ ), condition.

#### 4.5. Discussion

In a probabilistic spatial SRT task the consequences of introducing a secondary colour cue (incidental to participants' responses) were assessed by comparing two colour presentation conditions (Blocked and Mixed) with a monochrome baseline. Results indicate that while learning occurred in all conditions, it was greatest in the standard monochrome version. Therefore, although it is possible to attend to additional information sources whilst performing an SRT under the current stimulus configurations they produce a cost for the performance of the main task rather than a benefit. Whilst there were weak indications of a small degree of awareness in the recognition and PDP tasks the magnitude of these effects

did not vary across the viewing conditions. This suggests that it was unlikely participants adopted a more intentional strategy of learning following the introduction of colour information.

One possible reason for the absence of any benefit to learning is that the colours acted as a distraction removing resources from the primary task. Although, many researchers have claimed that attention is not required for SRT learning (Curran & Keele, 1993; Keele et al., 2003) it has been reported that load in the SRT affects secondary tasks, which suggests a role for attention (Rowland & Shanks, 2006a; Shanks et al., 2005). Nonetheless, if attention is being diverted to the colours (possibly automatically) the results indicate some independence in processing of the colour and spatial properties of the stimuli. Alternately, the degree of processing of the colour cue, though sufficient to attenuate performance, might be relatively low due to its perceived irrelevance and so participants' active suppression of that cue. Another possibility is that the processing demands are greater for two properties with different stimulus dimensions presented simultaneously compared to properties with a common dimension (e.g. two locations) presented over time. There is, of course, evidence for a separation in the processing of spatial (or action related) visual information and identity related information (Goodale & Milner, 1992; Mishkin, Ungerleider, & Kathleen, 1983).

The next study examines the effects of addressing a secondary cue (vertical location) which is within the same stimulus dimension as the primary cue. Therefore, it is less likely to be processed entirely independently of the primary cue. Additionally, a number of researchers have argued that spatial cues are special in the SRT task, but debated whether this is due to their direct correspondence with the response keys or some other property (e.g. learning sequences of apparent motion) (Koch & Hoffmann, 2000a, 2000b).

#### **4.6. Experiment 2**

The second experiment examined whether the addition of a secondary spatial cue could modulate sequence learning in a spatial SRT task. To do this a novel variant of the SRT was developed in which participants viewed a four by four grid of spatial locations and responded to the appearance of a cross in one of the squares by pressing the button associated with its horizontal location, which as within all tasks were based on a probabilistically presented SOC sequence. The secondary cue was the vertical location of the stimulus, and the experiment again contrasted conditions in which this cue was organised in different ways with a baseline (where the vertical location did not vary across trials). The aim was to examine whether the integration of this secondary cue into the learning of the sequence might be facilitated either because both primary and secondary cues possessed a

common stimulus dimension or because spatial cue are of special importance. Importantly, in the current design there is no direct association between the secondary spatial cue and the spatial distribution of responses, unlike the primary cue of horizontal stimulus locations and the horizontal arrangement of the response buttons. Therefore any effect cannot be simply due to an automatic priming of congruent spatial dimensions between the stimulus and response (Bischoff-Grethe et al., 2004; Kornblum et al., 1990; Ziessler, 1994).

The second experiment also introduced a number of other important enhancements to the design and procedures from experiment one. First, in addition to the Block and Mixed conditions used previously a new condition in which the secondary cue was entirely random was introduced. This allowed separation of any effects simply due to the salience of the secondary cue (e.g. distraction or enhanced vigilance) rather than its relationship to the sequence structure. Second, further measures were introduced to examine the effects of the secondary cue on sequence learning by assessing the impact of removing the secondary cue in two transfer blocks in the late stages of training. In the first transfer the location cue was randomised and in the second the vertical shifts were removed. The aim was to examine whether performance was disrupted by both covert and overt removal of the secondary cue. This was done because it was felt whilst participants might utilise and depend upon the secondary cue it might not exert a strong enough effect upon learning to be apparent.

Finally, the experiment assessed once again whether the introduction of a secondary cue was more likely to lead awareness of the sequence structure than in standard conditions.

## **4.7. Methods**

### **4.7.1 Participants**

44 Brunel University undergraduate, 36 female and 8 male (mean age 19.3 SD=1.1) gave informed consent to participate in the study for course credits.

### **4.7.2. Stimuli and Materials**

Participants viewed 16 locations denoted by black outline squares (21mm by 21mm) arranged in a four by four grid on an even white background. All squares were evenly spaced (13mm) both horizontally and vertically. The current location was denoted by the appearance of a black cross. The horizontal location of the stimulus was determined using exactly the same SOC sequences constructed for experiment 1. However, the additional locations allowed the introduction of a secondary spatial cue (vertical location), which was again incidental to the primary task (i.e. responding to the horizontal location). In spatial cue

conditions four vertical were distributed across the SOC sequence so they occurred only once at each of the four possible locations (see table 4.2). Hence, the combination of vertical and horizontal location unambiguously identified the next location. By using four levels vertical locations (instead of the three employed in the colour experiment) the magnitude of vertical and horizontal displacement could be balanced, but not all vertical location combinations were used. There were four experimental condition which differed in the presentation of the secondary spatial cue, Blocked (vertical locations of sequence items are presented in chunks), Mixed (vertical locations are distributed over the sequence), Random (the secondary cue was random but constrained to prevent location repeats) and No-Cue (a horizontal SRT with no vertical displacement between items during a block of trials). The vertical locations used in the blocked and mixed condition are illustrated in table 4.2.

**Table 4.2,** Detailing the construction of the secondary spatial cue for the Blocked and Mixed conditions. Colours are used to denote the vertical location (row); Green=1 (top row), Blue=2, Red=3 and Yellow=4 (bottom row).

Spatial Cue	SOC1	SOC2
Blocked	421341231432	431241321423
Mixed	421341231432	431241321423

### 4.7.3. Design and Procedure

Participants were assigned to one of four experimental groups and instructed to respond when an x symbol appeared in one of the 16 squares on the screen by pressing the button corresponding to its horizontal location. The procedure followed was similar to experiment 1 with the following exception. For participants in the baseline none secondary cue condition the vertical location was still shifted but only for every block of 100 trials (by repeatedly cycling through the four rows in a random order).

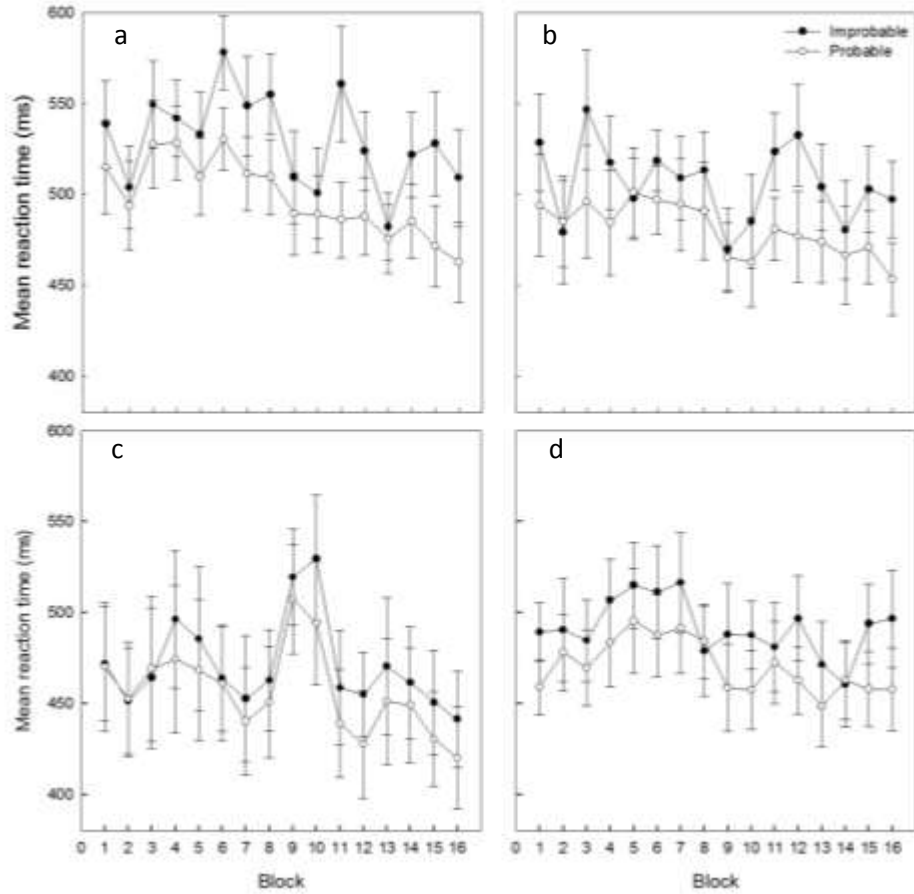
Each participant completed 16 blocks of 100 trials with a short break between each block. Blocks 1-8 were designated learning blocks, blocks 9-10 and 13-14 were transfer blocks (in which the secondary cue was disrupted or removed) and blocks 11-12 and 15-16 returned to the same learning task as 1-8. In one transfer block the vertical location cue was removed (e.g. the sequence was presented in a single row) and in the other the vertical location was randomised (with the constraint that it could not repeat the last vertical row). The randomisation transfer was performed slightly differently in the blocked condition in which each time a new chunk was selected a random vertical row was assigned to the three item

chunk (i.e. trials repeat in the same row) to minimise the likelihood of participants becoming aware of a change in the nature of the stimulus. The order of these transfers was counterbalanced across participants. Basic analysis of learning was again based upon mean RTs from blocks 5-8 and also the effects of the transfer blocks. Exclusion criteria were as for experiment 1.

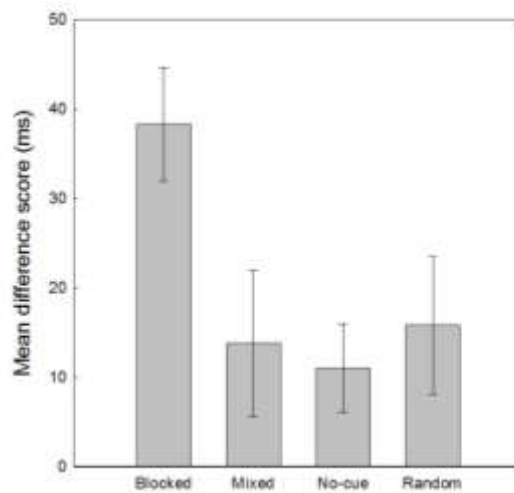
Awareness was tested using the recognition test using the same procedures as outlined in experiment 1.

#### **4.8. Results**

Figure 4.5 depicts the mean RTs in each block for the No-cue (fig. 4.5a), Blocked (fig. 4.5b), Mixed (fig. 4.5c) and Random (fig. 4.5d) vertical location conditions. A 3-way ANOVA was performed using mean RTs with Probability (probable vs. improbable) and Block (Blocks 5-8) as within groups factors and Spatial Condition (No-Cue, Blocked, Mixed and Random) as between groups factors. All four experimental groups showed learning (Probability:  $F(1,40)=32.746, p<.001$ ). However, there was again a variation in the magnitude of learning between the different viewing groups (Probability x Spatial Condition  $F(3,40)=3.293, p=.030$ ). To assess the basis of this interaction for each of the four conditions the mean learning score (improbable minus probable RTs) across all four training blocks was calculated and independent t-tests were used to compare the conditions. Learning was considerably higher in the Blocked condition compared to the No-cue ( $t(20)=3.384, p=.002$ ), Random ( $t(20)=2.256, p=.018$ ) and Mixed ( $t(20)=2.369, p=.014$ ) conditions. No other conditions significantly differed (see fig. 4.6). Again, t-tests were also performed to identify whether learning was significantly different from zero. One tailed t-tests revealed that learning in the Blocked ( $t(10)=6.038, p<.001$ ), No-cue ( $t(10)=2.224, p=.025$ ) and Random ( $t(10)=2.063, p=.033$ ) were significant. However, the Mixed condition ( $t(10)=1.691, p=.061$ ), only revealed a trend towards significance. None of the other ANOVA effects were significant or showed a trend.



**Figure 4.5.** Mean RTs broken down by block and probability for Blocked vertical (a), Mixed vertical (b), No-cue vertical (c) and Random vertical (d) conditions. Error bars represent 1 SE.



**Figure 4.6.** Graph containing mean learning scores for blocks 5-8 for all four conditions in the Spatial task. Error bars represent 1 SE.

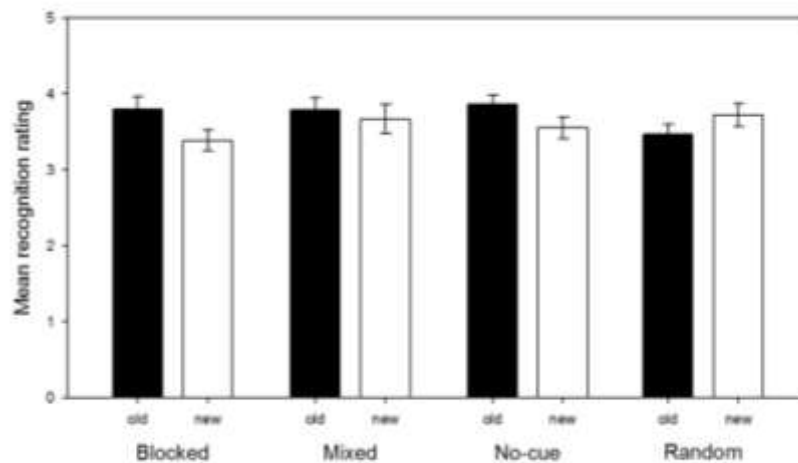


To further examine the possible effects of the secondary cues on learning the effects of two transfer conditions were assessed. In the first the vertical cue was randomised so that it was still apparently present but no longer informative regarding the identity of next location, and in the second the vertical cue was entirely removed (in this case stimuli appeared in any of four boxes on a single vertical row). Two blocks of each transfer condition were performed and so RTs were pooled across both blocks and compared with mean performance in the standard training blocks immediately before and after transfer. Both transfer conditions were analysed with a 3-way ANOVA with Probability, Stimulus Transfer (Transfer vs. Training) and spatial cue condition. Cue conditions in which the transfer represented no change from the training block (the random vertical and no-cue conditions) were excluded from the analysis of the relevant transfers. Following both types of transfer participants still showed learning across all conditions (Probability:  $F(1,30)=36.934$ ,  $p<.001$  (vertical transfer) and  $F(1,30)=35.102$ ,  $p<.001$  (no-cue)) but there was no evidence for any overall difference in learning across spatial cue conditions (Probability X Spatial Cue condition:  $p>.1$ ). However, randomising the vertical cue did lead to a decrease in the magnitude of learning across all cue conditions (Probability X Stimulus Transfer:  $F(1,30)=4.774$ ,  $p=0.037$ ). Both the randomisation and removal of the vertical cue led to a dramatic change in participants reaction times (Stimulus Transfer:  $F(1,30)=29.460$ ,  $p<.001$  and  $F(1,30)=31.234$ ,  $p<.001$ ), but in opposite directions with the randomisation of the cues producing slower RTs (mean change  $-32.7\text{ms}$ ) and the removal of the cue producing faster responses (mean change  $36\text{ms}$ ). After transfer to a random cue this effect was strongly modulated by introduction of a constantly changing vertical location to the no-cue condition (Stimulus Transfer X Spatial Cue condition:  $F(2,30)=21.425$ ,  $p<.001$ ). Critically, the removal of the vertical cue had a different effect on learning depending on how secondary cue had been presented during training (Probability X Stimulus Transfer X Cue condition:  $F(2,30)=3.301$ ,  $p=0.051$ ). This was attributable to the random vertical location condition being significantly less affected by the removal of the vertical location changes than the Blocked ( $t(11)=2.662$ ,  $p=0.015$ ) condition and showing a trend to be less effected than the mixed condition ( $t(11)=1.747$ ,  $p=0.098$ ).

In order to assess whether the blocked vertical condition promoted chunking of items in memory additional post-hoc analysis was performed on the responses in this condition. Mean RTs for locations within and across chunks were calculated. A 2-way ANOVA, with Transition Type (within vs. across spatial chunk) and Block (5-8) as within participant factors, found no evidence for an overall difference between RTs within and across spatial chunks (Transition Type:  $p>.1$ ), which indicates little evidence of representations of these

chunks. However, there was an increase in reaction times over the 4 training blocks (Block:  $F(3,30)=4.739, p=.008$ ) and a difference in the way RTs changed across blocks for the two chunking conditions (Block X Transition Type:  $F(3,30)=3.675, p=.023$ ). Paired sample t-tests indicated the difference was due to a trend ( $t(10)=2.194, p=0.053$ ) for faster RTs when crossing chunks compared to transitions within chunks in the earlier part of the training phase (block 5), which disappeared as RTs became faster (all other t-tests were non-significant  $p>.1$ ).

Finally, awareness ratings were classified on a six-point scale as within experiment 1 (see fig. 4.7). A 2-way ANOVA was performed with Sequence type (Old vs. New) and Cue Condition (Blocked vs. Mixed vs. No-cue vs. Random) as factors. Participants displayed some degree of ability to discriminate between the Old and New sequences (Sequence type:  $F(1,40)=4.834, p=.034$ ). Overall ratings were the same across all Cue conditions (Cue Condition:  $F(1,40)=.088, p=.869$ ). Nonetheless, there was a difference in the relative scores for old and new sequences dependent upon the vertical cue condition Sequence type x Cue Condition:  $F(3,40)=3.554, p=.023$ ). Paired sample t-tests revealed that in No-cue ( $t(10)=2.275, p=.023$ ) and Blocked ( $t(10)=1.934, p=.041$ ) conditions old sequences scored significantly higher than new whilst the Random ( $t(10)=-1.811, p=.050$ ) condition showed the opposite effect.



**Figure 4.7.** Mean recognition ratings for Old and New sequences for all four Spatial conditions. Error bars represent 1 SE.

Testing scores in all conditions against chance performance levels revealed above chance performance for Old sequences in the No-cue condition ( $t(10)=1.955, p=.040$ ) and trends towards significance for old sequences in the Blocked ( $t(10)=1.718, p=.059$ ) and Mixed

( $t(10)=1.794, p=.052$ ) conditions. For the new conditions only the Random condition showed even a trend towards deviating from chance ( $t(10)=1.477, p=.086$ ) but as this was above the mid-point it indicated a bias away from correct identification.

#### **4.9. Discussion**

The current experiment clearly demonstrates that sequence learning in a SRT task can be enhanced by a secondary spatial cue when the cue is grouped into blocks of the same type. However, the absence of any difference in RTs within and across blocks of vertical locations suggests that participants are not chunking based on these subdivisions of the secondary cue, but utilising the cue information in some other way. Furthermore, when the cue was removed there was only a weak attenuation of learning and this was equally great in all conditions. This might indicate that the effects of the secondary cue are to enhance the process of learning, but that they are not subsequently necessary for producing learning.

An important issue to be addressed is how the secondary cue contributes to learning in the current study, but not in the first experiment. Part of the explanation may be due to the differences in the relationships between the secondary and primary cues. In the first experiment the greatest benefits were found in the monochrome condition and learning was attenuated in the secondary cue conditions, which suggests they placed demands upon processing resources. However in the current experiment, participants at worst performed at similar levels to the non-cue condition when the vertical cue was mixed or random, but also benefited considerably in the blocked condition. This suggests a greater ability to suppress the cue if it was not helpful, and utilise it when needed. One major difference between the experiments was that in the current one two spatial sources of information are used and so likely to engage overlapping networks of activity in higher visual areas to a greater degree than perceptual and spatial cues used in the primary experiment. This opens the question of whether similar effects might be found if both cues had a perceptual basis, which is addressed in the next experiment.

Part of the reason that the vertical cue was exploited in the blocked condition may simply be it was simply more salient that a pattern was present when the cue was presented in groups. However, in that circumstance it might be expected that those chunks would be easier to recall, but that was not the case. Interestingly, there was an indication that in the early stages of learning transitions between blocks were better encoded than transitions within chunks. This might indicate that it was the salience of changes in vertical location that aided learning and that it was the relative low-frequency with which they occurred in this condition that made them especially salient. An alternate possibility is that learning is partially promoted

by learning sequences of eye-movements and that is easier when the movements are more structured, e.g. scanning horizontally with occasional vertical shifts is analogous to eye movements in reading.

Interestingly, performance in the baseline (no-cue) condition was lower than in the first experiment. However, the vertical location of this cue was varied from block-to-block, which suggests that consistency in the precise spatial location of the stimulus across the training period might be crucial. Alternately, participants may simply spread their attentional processing over the other whole of the highlighted array of locations, and so reduce attention to the primary task.

An additional feature of the results was the opposing direction of the effects of transfer. The disruptive effect of the randomisation of the vertical cue indicates that this cue was at least partially processed in both vertical cue conditions, even if it only affected learning in the blocked condition. However, the hints of enhanced learning after the removal of the vertical cues suggests that although the vertical cue may promote learning they may also produce a cost once learning is established.

There was weak evidence for a degree of awareness in all conditions as Recognition scores were generally higher for Old sequences than New, but the only condition to differ from significantly from chance in awareness testing was the no secondary cue condition. This might indicate that there are greater task demands in the secondary cue conditions possibly from the need to process the additional information, and this reduces participants' ability to be able to intentionally seek to identify sequence patterns.

#### **4.10. Experiment 3**

In two experiments strikingly different results with regards to the effects of a secondary cue in a spatial SRT task were found. When a non-spatial perceptual property (colour) was used as a secondary cue it interfered with learning, whilst a non-behaviourally relevant spatial cue (vertical location) either had no effect or when presented in blocks enhanced learning. The final experiment examines whether secondary cues can be utilised if the spatial component of the task is entirely removed and participants are forced to respond based on perceptual cues. In this case, participants cannot use spatial formations to respond but must instead learn representations based on the arbitrary association of shapes and motor responses. Importantly, both cues are non-spatial perceptual properties of the stimuli and so the experiment will help to clarify if previous results were a consequence of shared stimulus

dimensions or specific to the processing of the selected stimulus dimensions in the SRT. This will depend if the results most closely resemble experiment 1 or 2.

The methodology employed was similar to experiment 2, but as this task involves learning of an S-R mapping as well as that of a sequence, participants were provided with additional training trials to achieve an appropriate level and so only performed one transfer (random cue). However, it is possible that a more difficult task will require more attention, which either may attenuate processing of the secondary cue if they are largely processed independently (Rowland & Shanks, 2006a, 2006b) or if the two cues are inherently bound together it may increase the chances of participants becoming aware of the secondary cue structure.

## **4.11. Methods**

### **4.11.1 Participants**

44 Brunel University undergraduate, 40 female and 4 male (mean age 19.2, SD=2.2), gave informed consent to participate in the study for course credits who were again excluded if self-reporting colour blindness.

### **4.11.2. Stimuli and Materials**

Participants viewed a single black outline square in the centre of the screen and for each trial a shape cue (a square, triangle, circle or cross) was displayed. The distribution of the sequences of shapes was determined by the same SOC sequences used previously. A template was placed over the buttons of response box indicating the correspondence between buttons and shapes. The secondary cue of colours had four levels (Blue, Green, Yellow and Red) and was presented in the same four conditions used in experiment two (Blocked, Mixed, Random and No-Cue). The correspondence between primary and secondary cue was determined in exactly the same way as outlined in experiment 2.

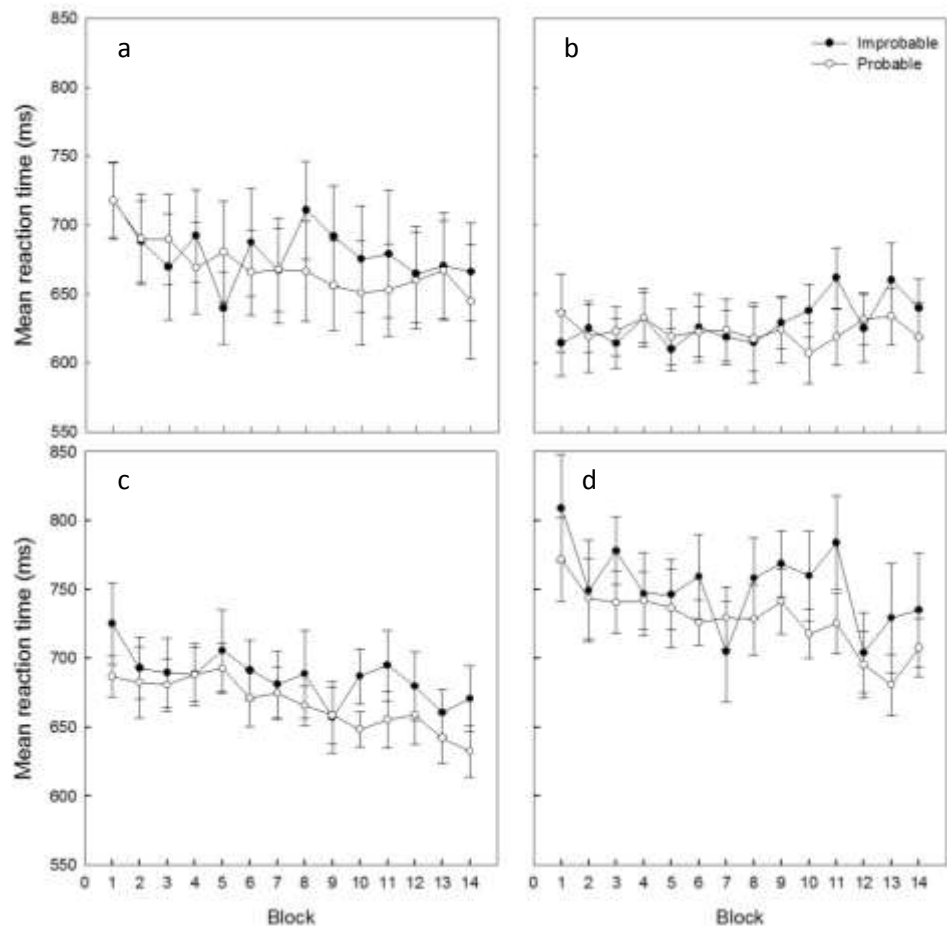
### **4.11.3. Design and Procedure**

The procedure followed was similar to previous experiments with the following exceptions. Participants were assigned to one of four secondary cue groups (Blocked, Mixed, Random and No-Cue) and instructed to respond when a shape appeared on the screen by pressing the associated button as quickly. The mapping between response keys and shapes was counterbalanced across participants and they completed 100 random practice trials to consolidate the mapping before the training phase. Participants in each condition performed

14 blocks of 100 trials. The first ten blocks were a training phase (extended from the second experiments due to the potentially increased difficulty of the task), 11-12 transfer (colour cue randomised) and 13-14 return to training. Exclusion criteria were unchanged.

Awareness was assessed using the recognition task.

#### 4.12. Results



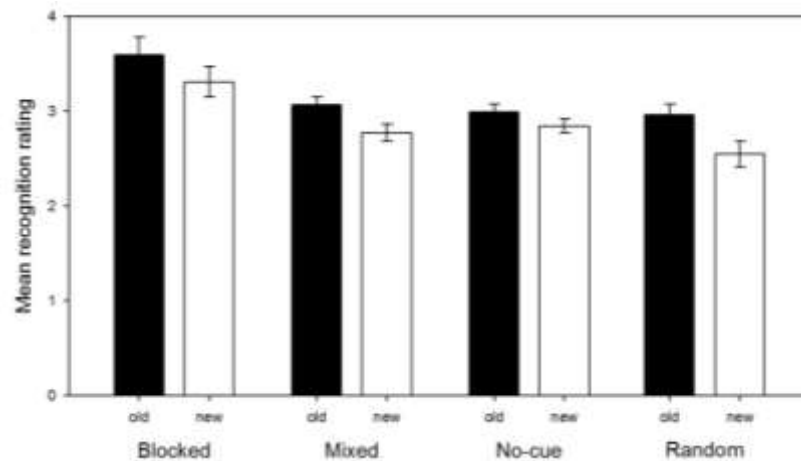
**Figure 4.8.** Mean RTs broken down by block and probability for Blocked (a), Mixed (b), No-cue (c) and Random (d), conditions. Error bars represent 1 SE.

Figure 4.8 depicts the mean RTs in each block for the No-cue (fig.4.8a), blocked (fig. 4.8b), mixed (fig. 4.8c) and random (fig. 4.8d) colour conditions. A 3 way ANOVA was performed using mean RTs with Probability (probable vs. improbable) and Block (Blocks 7-10) as within groups factors and Cue Condition (No-cue, Blocked, Mixed and Random) as between groups factors. Once again learning had taken place across cue conditions (Probability:  $F(1,40)=10.793, p=.002$ ), but there was no indications of any differences in the magnitude of learning between conditions (Probability x Condition:  $F(3,40)=.579, p=.632$ ). Additionally, overall RTs were different across conditions (Condition:  $F(3,40)=4.175, p=.012$ ). Paired

sample t-tests indicated that RTs in the Random were slower than both the Mixed ( $t(20)=3.99, p<.001$ ) and No-cue ( $t(20)=2.465, p=.012$ ) conditions and that the Mixed was faster than the No-cue ( $t(20)=-1.899, p=.046$ ). There was also an interaction between Probability x Block ( $F(3,120)=2.841, p=.041$ ), indicating that as expected learning increased across blocks (fig. 4.8).

To further examine the possible effects of the secondary cues on learning the results of transfer to a random cue was assessed in exactly the same way as experiment 2. The only effect that was significant was that participants showed learning across all conditions (Probability:  $F(1,30)=22.845, p<.001$ ) but there was no evidence for any overall difference in learning across cue conditions either alone or in combination with other factors. The Blocked colour condition was again analysed separately for evidence of chunking of the colour groups. Perhaps surprisingly RTs were generally slower for responses within colour chunks compared to those crossing colour chunks boundaries (Transition Type:  $F(1,10)=7.979, p=.018$ ), but there were no other significant main effects or interactions.

Finally, awareness ratings were classified as in the previous experiments. A 2-way ANOVA with Sequence type (Old vs. New) as a within groups factor and Colour condition (No-cue vs. Blocked vs. Mixed vs. Random) as the between groups factor was performed. There was a robust difference in the mean scores for old and new sequences (Sequence type:  $F(1,40)=21.53, p<.001$ ), but this difference was similar across all cue conditions (Sequence type x Colour condition:  $F(3,40)=.53, p=.6.7$ ). There was also no overall difference in ratings across cue conditions (Colour condition:  $F(3,40)=1.58, p=.21$ ). Testing against chance performance revealed that for old sequences scores in the No-cue ( $t(10)=2.362, p=.020$ ) and Mixed ( $t(10)=3.276, p=.004$ ) conditions were significantly above the mid-point and there was a trend towards significance in the Random ( $t(10)=1.393, p=.097$ ) condition (fig. 4.9). Furthermore for New sequences only the Random ( $t(10)=-1.884, p=.045$ ) was significantly below the mid-point but the Blocked ( $t(10)=-1.462, p=.087$ ) condition showed a trend in that direction.



**Figure 4.9.** Graph depicting mean recognition scores for Old and New sequences. Error bars represent 1 SE.

#### 4.13. Discussion

The magnitude of learning SRT in which stimuli are encoded entirely by non-spatial perceptual cue was unaffected by the presence of a secondary perceptual cue. Overall, despite an increase in mean RTs there was a lower magnitude of learning than within previous experiments (Blocked, 26ms, Mixed, 7.1ms, Monochrome, 17ms and Random, 18.7ms), which likely reflects the dual task costs resulting from the need to also learn the arbitrary stimulus response mapping and supports the proposal that attention plays a role in the SRT (Mayr, 1996; Remillard, 2009; Rowland & Shanks, 2006a). The attenuation in learning occurred despite participants being given 200 more training trials than in the earlier experiments (intended in part to offset the increase task difficulty). Furthermore, there was also no evidence that randomising the secondary cue had any (positive or negative) effect on learning in any of the cue conditions.

Therefore, the results in this study differed from the experiments those in experiment 1 and 2, which showed a cost and benefit to secondary information respectively. It is necessary, therefore, to consider the reasons for the absence of such effects in this study. First, it is possible that performing the primary task was too demanding for participants to have additional resources to process the secondary stimulus. This would suggest that cueing attention to the relevant dimension attenuates processing of the other dimension and might indicate that the processing of the secondary dimension is largely automatic (rather than strategic). Second, it remains possible that spatial information is special in the degree to which it facilitates learning in the SRT task, which is considered further in the general discussion. Third, if participants had been allowed to learn for longer group based



differences may have emerged with the increased magnitude of learning. However, it should be noted that there were no hint of any group differences in the statistics.

Furthermore, when examining chunking effects the pattern of results found was different from previous experiments as fastest RTs occurred for transitions between chunks rather than within chunks. In the second experiment, this occurred early within learning and then disappeared, which would suggest learning is occurring at a slower rate in the current experiment. An explanation of the finding is that despite the high primary task demands the colour transition resulted in increased attention and so enhanced relative salience of those transitions, which might have been especially true if the task demands withdrew attention in other conditions.

Finally, analysis of the recognition scores indicated some evidence for a degree of awareness of the primary sequence structure as scores differed between old and new sequences, which again could have resulted from increased attention to the primary task. However, the scores themselves did not differ significantly chance levels and so any interpretation has to be made with caution.

#### **4.14. General Discussion**

Across three experiments the effects on sequence learning of non-behaviourally relevant (but potentially informative) secondary cues were examined. The experiments systematically varied the relationship between the perceptual and spatial dimensions of the primary behavioural and the secondary cues. In the first experiment a secondary perceptual cue (colour) impaired learning in a spatial SRT task when compared with a traditional monochrome baseline, whether it was presented in the main sequence in blocks or mixed throughout. The results indicate that the additional information may have distracted participants from the primary 12 item sequence. This may have resulted from either a strategic attempt by participants to engage in strategies using the secondary cue or whether the perceptual salience of the cues attracted attention automatically in a bottom-up manner. Nevertheless, significant learning of the sequence was present in all three conditions, meaning that even if the secondary cue acted as noise, participants were able to learn in its presence and is consistent with previous reports of dual-task costs in SRT learning (Rowland & Shanks, 2006a; Shanks et al., 2005). In the second experiment a secondary spatial cue (vertical location) enhanced learning in a spatial SRT when the cue was systematically grouped into blocks of the same vertical locations. However, learning was indistinguishable when changes in the vertical location were mixed throughout the sequence, occurred entirely randomly or merely changed across blocks of 100 trials, which indicated the effect was not

simply due to an alerting effect of the location changes. In the third experiment, no effect on learning was found for a secondary perceptual cue (colour) when the primary SRT was also based upon a perceptual cue (shape). Though, learning was generally reduced in this experiment in comparison with the first two, which indicates that it was a more demanding task and so might have reduced the available resources for processing the secondary cue.

An interesting feature of the results is the restriction of the enhancement of learning to blocked presentations of locations in the second experiment. Koch and Hoffman (2000b) have argued that the regularities in the presentation of the sequence structure can promote the formation of chunks in learning sequences. In their study they compared the effects of learning in sequences with either a strong (triplets of sequence items presented in ascending or descending order) or weak (an arbitrary relationship between successive items) perceptual structure, and by manipulating the mapping of the stimulus to the response key they were able to create or disrupt triplets in the response sequence for either of the perceptual conditions. They reported that chunking was apparent for either perceptual configuration if the responses were strongly structured (e.g. responses occurred in ascending or descending order). Their deterministically presented sequence may favour the use of motor responses as a basis of learning and this differs from the current study's probabilistic presentation, which cannot be completed by reproducing chains of responses. Importantly, the results of the second experiment did not support the view that the sequence was represented as chunks based upon the secondary cue as learning was highest for the first item within a chunk rather than later ones. This suggests that it was the transitions across chunks that were especially salient to participants. It would be interesting to know that if the locations had cycled through a regular series of changes (rows 1, 2, 3, 4 or 4, 3, 2, 1) whether this would have promoted better learning by creating increased transitions but in a highly structured manner. An alternate view is that chunking stimuli into transitions within rows matches the normal way we scan a visual scene.

Nonetheless, the current experiments support the view that spatial cues may be especially important in the production of learning within the SRT as they facilitated learning whilst secondary perceptual (colour) cues either had no effect (when the primary cue was perceptual) or interfered with learning (when the primary was spatial). However, in contrast to Koch and Hoffman (2000a, 2000b) these findings suggest the effect is not dependent upon priming of responses as it can occur on a perceptual basis even when the relationship between the spatial cue and response is arbitrary (e.g. the effect of vertical location on horizontally mapped responses). In part, the positive effect found in the spatial condition may be due to the ability to integrate information with common stimulus dimensions though

the nature of this common dimensionality may be broader than previously thought. In general earlier studies emphasising the importance of common dimensions have considered it as a precise correspondence between the stimuli and response (e.g. spatial compatibility between stimulus locations and response keys) (Koch & Hoffmann, 2000a; Lungu et al., 2004), but placed less emphasis on the integration of multiple perceptual dimensions. The ability to integrate non-behaviourally relevant spatial information suggests that the concept may be broader than previously considered.

Nonetheless, the third experiment offered no evidence that two perceptual cues could be integrated in the same way as the spatial cues. This might point to limits on the concept of common dimensions, which needs to be more clearly defined. However, the interpretation of this experiment was complicated by the fundamental increase in difficulty in the basic performance of the SRT based on arbitrary associations rather than spatial locations. Hence, learning may have needed much longer to develop and allow differences between conditions to be measured. Also, the demands of attending to the shape may have prevented attendance to colour. This view is, in part, supported by the costs on learning that a perceptual cue induced in the first experiment, which is certainly consistent with competition for processing resources between primary and secondary tasks. It is also possible that in the locations task (experiment 2) spatial coordinates may automatically be encoded in two or three dimensions (as localisation in one dimension is rarely important in the real world) and so it is not necessary to separately process each dimension. Further experimentation with perceptual cues is required to determine if they can be combined and under what circumstances that might occur.

Across all experiments there was limited evidence for a degree of awareness as participants were frequently slightly better at identifying familiar sequences presented in training than less familiar ones. However, when ability to recognise sequences was tested against chance performance it was rarely significant. There was also no evidence of the awareness being modulated by the secondary cue. Perhaps, this is slightly unsurprising as the only enhancement for learning occurred in the spatial cue condition and these are likely to be primarily processed within the dorsal visual processing stream, which is generally argued to occur in the absence of awareness (Milner & Goodale, 1995). The implications of this are considered further in the General discussion (See chapter 7 section 7.4.).

In conclusion, the results of the present three studies indicate that secondary spatial information may enhance sequence learning, but only if the primary task is also specified by spatial information. When the secondary cue is a perceptual one it causes a cost in a spatially

specified learning task, and showed no affect for a perceptually specified learning task. However, the configuration of the secondary cue might have important implications and needs to be investigated in future studies.

## Chapter 5

### V. Levodopa medication improves sequence learning on the serial reaction time task in Parkinson's disease

#### 5.1. Introduction

Levodopa medication has been described as the most significant advance in the treatment of Parkinson's disease (PD) (Olanow et al., 2004; Poewe, Antonini, Zijlmans, Burkhard, & Vingerhoets, 2010; Stocchi, 2005). By ameliorating the effects of dopamine depletion within the basal ganglia, levodopa can produce a reduction in the major motor symptoms with considerable benefits for patients' quality of life. Nonetheless, with chronic use, levodopa can produce side-effects that affect the motor system (e.g. dyskinesias), cognitive function and behaviour (e.g. compulsive behaviours). Levodopa produces a widespread increase in dopamine levels across the whole brain in PD and not merely in those pathways where dopamine production is impaired. As a consequence, in relation to cognition, those fronto-striatal circuits that are relatively spared by the effects of the disease in the early stages may have an excess of dopamine, and as a result of this 'dopamine overdose' may impair functions mediated by these circuits (Gotham, Brown, & Marsden, 1988). The action of dopamine within a particular brain area may be optimal in a specific operating range. The relation of dopamine to performance is described by an inverted U curve, where too little or much dopamine may be detrimental to performance (Cools, Barker, Sahakian, & Robbins, 2001; Goldman-rakic 1999; Williams & Goldman-rakic, 1995). As a consequence, it is very difficult to predict the extent and direction in which levodopa medication will modulate, positively or negatively, specific cognitive processes. Therefore, studying such effects has potentially important implications for the management of PD as well as increasing our theoretical understanding of the role of dopamine in modulating cognition.

While dopamine has been shown to be involved in a variety of tasks, it is widely recognised to have a particular importance in reinforcement learning and working memory (Cools et al., 2001; Lange et al., 1992; Moustafa, Cohen, Sherman, & Frank, 2008). For example, in a within groups study of participants tested both on and off levodopa medication, it was discovered the l-Dopa improved response initiations for visuospatial memory and extra-dimensional matching tests (Kulisevsky et al., 1996). Furthermore, patients with PD perform better when taking l-Dopa medication than when they are not during intentional step by step learning, where they are provided rewards based on their performance (Shohamy, Myers, Grossman, Sage, & Gluck, 2005). In this case, PDs who were off medication learnt small chains of typically 2-3 locations to reach their reward but were not capable of learning longer

chains. Shohamy and colleagues (2005) speculate that the reason for this may be that working memory capacities in PD are impaired and so limited to 2-3 item chunks. On the other hand, PDs on medication performed comparably to controls. However, as this was an intentional reward based system, it is likely that these findings are driven by dopamine reward mechanisms, where participants perform better due to positive reinforcement (Wolfram Schultz, 2002). Nevertheless, the importance of dopamine release in the basal ganglia and its dysfunction in PD during a spatial working memory task has been demonstrated using PET (Sawamoto et al., 2008). Using  $^{11}\text{C}$ -raclopride (an injected ligand which binds to D2 dopamine receptors but is competitively displaced when dopamine is released) scans of healthy participants as well as those with PD, the authors discovered that binding of receptors in the dorsal caudate was reduced for the control group during the working memory task (in comparison to a visuomotor task). However,  $^{11}\text{C}$ -raclopride binding was not reduced in PD. The authors demonstrate the dopamine release is significantly reduced in the PD group in comparison to controls in the dorsal striatum but not in the medial pre-frontal area. These studies suggest that attenuated dopamine release is a significant factor in impaired learning on tasks sensitive to striatal functions. As demonstrated by some of these studies, PDs taking their prescribed medication may benefit during working memory tasks. However, its role in incidental processing is far from clear.

Accumulating evidence suggests that dopamine levels (especially within the basal ganglia) are crucial for procedural learning which occurs incidentally (Badgaiyan et al., 2007). Such learning has been widely investigated using the serial reaction time (SRT) task in which, over many blocks of trials, participants respond to the appearance of targets at one of four locations by pressing corresponding response buttons (Nissen & Bullemer, 1987). Unbeknownst to participants, these targets appear in a pre-determined sequence. Participants learn the sequence incidentally as evidenced by the speeding up of reaction times (RTs) on sequence relative to random or pseudorandom trials, without necessarily being aware of the existence of the repeating sequence, although mechanisms of intentional and explicit learning may be engaged if this sequence structure is insufficiently concealed. Studies in healthy participants have demonstrated the importance of dopamine during this type of sequence learning. First, a systematic release of dopamine in the anterior striatum and also the left caudate during performance of an incidental SRT task measured using PET, has been interpreted as facilitating the initiation of the specific movements required by the task and implicit rule learning respectively (Badgaiyan et al., 2007). Second, performance on a sequence learning task is impaired if the release of dopamine is inhibited by the administration of raclopride (a D2 receptor antagonist) (Tremblay et al., 2009). Furthermore,

the magnitude of the performance attenuation is related to the dose administered, indicative of an association between dopamine levels and sequence learning.

There has been considerable interest in studying the effects of PD on the SRT task. However, considerable variability in methodology and characteristics of the patient groups has resulted in some studies showing impaired learning (Brown et al., 2003; Carbon et al., 2003; Jackson et al., 1995; Kelly et al., 2004) whilst others report no differences (Doyon et al., 1997; Feigin et al., 2003) in performance from age matched controls. Nonetheless, a meta-analysis of incidental SRT studies in medicated PD patients by Siegert and colleagues (2006) provides strong support for the existence of performance deficits on this task in PD (Siegert, Taylor, Weatherall, & Abernethy, 2006).

An interesting study conducted by Muslimovic and colleagues (2007) recently assessed a large sample of PD patients (n= 95) after 6 learning blocks (block 7 being randomised) of a 10 item SRT task. They discovered that the patients displayed some learning of the sequence but that this was attenuated in comparison to healthy age matched controls. Furthermore, the authors assessed a subcategory of their PD sample to only include participants who were not receiving parkinsonian medication (non-medicated) at the time of testing. They discovered that this group learnt the sequence as well as controls (Muslimovic et al., 2007). However, the precise interpretations of the study are unclear due to the heterogeneous sample demographics that consist of fairly recently diagnosed patients (3.1 years), some of which are not medicated, ranging from stages 1-3 on the Hoehn and Yahr scale. Although the second analysis including only non-medicated patients is more evenly balanced, there is an even lower duration of illness (1.2 years). This combined with the fact that these patients have not been prescribed any parkinsonian medication suggests that their illness is not advanced enough to present any discernible effects in this domain. This is further reinforced by the similarly fast RTs in the non-medicated PD group when compared to controls.

However, an important study by Wilkinson and Jahanshahi (2007) demonstrated the existence of an impairment on the SRT task in PD patients (who were being treated with dopaminergic medication) while *off* dopaminergic medication indicating this impairment is a function of the disease and not simply a side effect of the medication (Wilkinson & Jahanshahi, 2007). One intriguing possibility raised by this study is that part of the variability of findings reported previously in PD is attributable to a partial amelioration of the SRT impairment by levodopa medication. However, there is considerable difficulty in determining the effects of dopaminergic medication on the incidental learning in SRT by directly comparing results across different studies due to the aforementioned variations in the

task procedures and the considerable inter-individual variability in the presentation of the disease.

In the current study, for the first time, a direct comparison of performance on the SRT task in the same group of PD patients tested both *on* and *off* dopaminergic medication to disentangle the effects of the disease and levodopa on incidental motor sequence learning. Although, previous studies have generated considerable insight into the neural mechanisms underlying SRT tasks, their implications for the likely effects of medication are less clear. Consistent with the emphasis on processing in the basal ganglia, functional imaging studies of incidental SRT tasks in healthy participants show increased activation within the caudate and putamen (Grafton, Hazeltine, & Ivry, 1995; Rauch et al., 1997; Schendan, Searl, Melrose, & Stern, 2003; Willingham, Salidis, & Gabrieli, 2002). However, these imaging studies have also linked incidental sequence learning to a wide network of brain regions associated with cognitive and motor control, for instance in cortical regions that are components of the fronto-striatal network including the pre and SMA (Grafton et al., 1995; Hazeltine et al., 1997; Honda et al., 1998) and the DLPFC (DLPFC). In addition, learning-related activation on these tasks is also seen in parietal areas and in the medial temporal lobes (Schendan et al., 2003). Essentially, the imaging results suggest that incidental sequence learning on the SRT is mediated by the motor circuit between the putamen and pre-SMA/SMA and the associative circuit between the caudate and the DLPFC. These are the core circuits adversely affected by dopamine depletion in PD (Alexander et al., 1986) and so might benefit from the administration of levodopa.

In the current study, the aim was to determine the relative effects of PD and levodopa medication on incidental motor sequence learning. Previous studies examining the effect of dopaminergic medication on sequence learning employed *intentional* sequence learning paradigms, with relatively simple deterministic sequence structures, which are highly likely to draw upon higher cortical areas such as the pre-frontal cortex in the learning process (Argyelan et al., 2008; Carbon et al., 2003, 2004; Ghilardi et al., 2003). In contrast, the current study employed a complex probabilistic sequence learning task, in which the sequence is very difficult to detect. The study compared the performance of the same patients learning parallel versions of probabilistic motor sequences while on or off medication. As learning on the task is likely to be mediated by the motor and associative fronto-striatal circuits, it was predicted that similar to the motor symptoms of PD, it would be improved on medication compared to the off state.



## 5.2. Methods

### 5.2.1 Participants

Fourteen individuals with a diagnosis of idiopathic PD (12 male, 13 right handed and one ambidextrous) aged between 54 and 75 ( $M = 66.8$ ,  $SD = 6.2$ ) participated in the study. All patients were recruited from the UCL Institute of Neurology and the National Hospital for Neurology and Neurosurgery. All patients met Parkinson's Disease Society Brain Bank diagnostic criteria for PD (Hughes, Daniel, Kilford, & Lees, 1992), and were screened for absence of dementia and major psychiatric illness. Disease duration ranged from 3 to 21 years ( $M = 8.9$ ,  $SD = 5.3$ ). Stage of illness was rated by a neurologist while patients were on their usual medication using the Hoehn and Yahr (Hoehn & Yahr, 1967) scale and patients were in the mild to moderate stages of the disease, with scores on the Hoehn and Yahr scale of 1 to 3 ( $M = 1.8$ ,  $SD = .7$ ). Severity of the motor symptoms of PD was rated while patients were off and on their usual medication using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS, part III Fahn & Elton, 2005). UPDRS motor scores ranged between 12 and 62 ( $M = 30.8$ ,  $SD = 13.8$ ) off medication and between 5 and 39 ( $M = 15.0$ ,  $SD = 8.8$ ) on medication. All patients were non-demented as demonstrated by scores  $>28$  ( $M = 29.4$ ,  $SD = .8$ ) on the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975). Patients were also screened for clinical depression indicated by scores  $> 18$  ( $M = 7.43$ ,  $SD = 3.7$ ) on the Beck Depression Inventory (BDI) (Beck, Erbaugh, Ward, Mock, & Mendelsohn, 1961). With regard to medication, the majority of the sample (12/14) were treated with levodopa (Sinemet, Madopar) and the mean levodopa equivalent daily dose (LEDD) was 1109.53 ( $SD = 802.3$ ) milligrams (Tomlinson et al., 2010). The study was approved by the Joint Ethics Committee of the Institute of Neurology and The National Hospital for Neurology and Neurosurgery. Informed consent was obtained prior to participation in the study from all patients. The travelling expenses of patients were reimbursed. Information about the patients is presented in Table 5.1.

**Table 5.1** Clinical characteristics and demographics of Parkinson’s disease patients who took part in the study.

<b>PD Patients (n = 14)</b>	<b>Mean</b>	<b>SDs</b>
Age	66.79	6.19
Disease duration	8.86	5.25
Unified Parkinson’s disease rating scale ON	15.00	8.75
Unified Parkinson’s disease rating scale OFF	30.79	13.81
Levodopa equivalent daily dosage	1109.53	802.33
Length of Medication Withdrawal (Hrs)	12.88	2.20
Hoehn and Yahr rating	1.75	0.67
Handedness	89.61	30.30
Years of Education	15.21	4.53
National Adult Reading Test	12.07	7.85
Beck Depression Inventory	7.43	3.65
Mini Mental State Examination	29.43	0.76

### 5.2.2 Apparatus and materials

For the incidental sequence learning task, stimulus presentation, response recording and RT measurement were all implemented on a laptop with a 17inch LCD monitor connected to a button box (see Chapter 2, figure 2.1). The four response buttons of interest were arranged in a row and will be referred to as 1-4 from left to right. Stimulus presentation involved four boxes arranged horizontally along the middle of the computer screen in white against a grey background. The boxes were 26 mm wide and 26 mm high with a separation of 16mm and an approximate viewing distance of 500mm.

### 5.2.3 Probabilistic Serial Reaction Time

The probabilistic SRT task comprised 15 blocks, each block with 100 trials during which participants were exposed to a four-choice SRT task. On each trial of the probabilistic SRT task, a black X appeared in the centre of one of the boxes, to which participants had to respond. Similar to the first experiment of chapter 3, two pairs of second order conditional sequences were used (pair 1 is SOC1 and SOC2, pair 2 is SOC3 and SOC 4, see chapter 2, sections 2.2. and 2.3. for more detailed explanation of methods).

Errors were signalled by a tone and each trial remained on the screen until the correct response was made. Trials were separated by an RSI of 400ms. Additionally, all reaction times over 2.5 standard deviations from each participants' overall mean RTs were excluded (ON medication = 2.4%, SD=.8 and OFF medication = 2.2%, SD=.7). These were considered to be outliers caused by momentary lapses of concentration and therefore removed as inaccurate readings. Consistent with previous studies (See Wilkinson & Jahanshahi, 2007), analysed RTs were comprised of both correct and incorrect responses. This makes allowance for the likelihood that a considerable number of errors, especially when off-medication, are likely to result from simple difficulties in kinetic control (i.e. multiple fingers are engaged per trial) rather than incorrect response selection.

#### **5.2.4 Tests of awareness of sequence**

*Process dissociation procedure:* To assess the degree to which participants were explicitly able to report the sequence structure the study employed two tests of sequence awareness, the Process Dissociation Procedure [PDP] (Jacoby et al., 1993; Jacoby, 1991) and a sequence recognition test. To maximise the likelihood that all SRT learning trials were learned implicitly these tests, which require the participant to be informed of the presence of a sequence, were only administered at the end of the second testing session. The PDP task was identical to the one presented in the first experiment of chapter 4 (see chapter 2, section 2.6 for a detailed description).

*Recognition test:* Similarly the recognition task was similar to the ones presented in chapter 4 (see chapter 2, section 2.7), with the exception that participants verbally expressed their confidence ratings.

#### **5.2.5 Procedure**

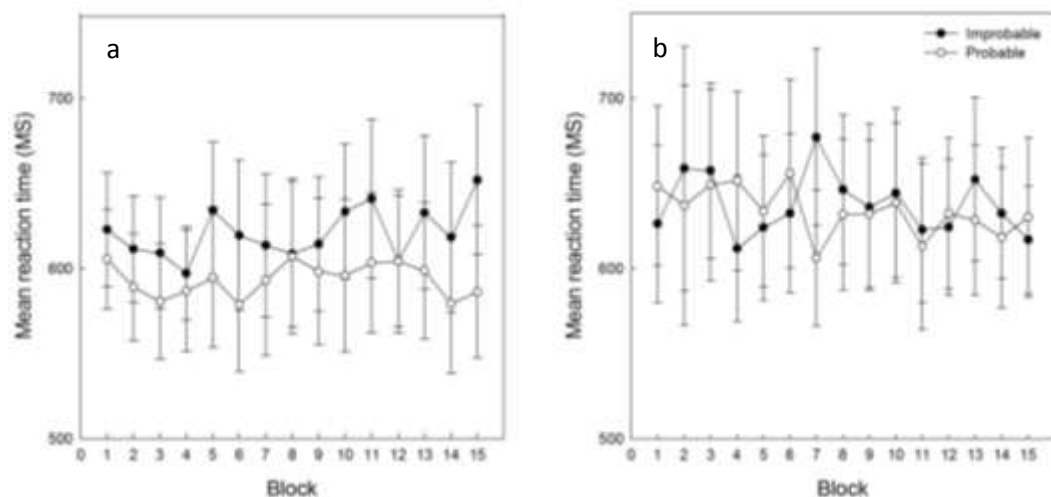
The study used a repeated measures design with all patients performing two incidental sequence learning testing sessions both on and off medication. The order in which participants performed the two medication conditions was counterbalanced, so that 50% performed on medication first. For each participant, the separate medication conditions were performed on two different days separated by at least one week with presentation of different pairs of parallel SOC sequences at each session.

To maximise the likelihood that all SRT learning trials were learned incidentally, the awareness tests, which require the participant to be informed of the presence of a sequence, were only administered at the end of the second testing session.

### 5.3. Results

#### 5.3.1 Probabilistic sequence learning

*Reaction times:* Figure 5.1 shows mean reaction times (RTs) for patients on (fig. 5.1a) and off (fig. 5.1b) levodopa medication across 15 blocks of trials. An ANOVA was performed on mean RTs with Medication (on vs. off), Probability (probable vs. improbable trials) and Block (1 – 15) as within subjects variables. This analysis revealed a significant main effect of Probability:  $F(1,13) = 7.50, p = .017$ , a significant interaction between Medication x Probability:  $F(1,13) = 6.71, p = .022$  and a significant interaction between Medication x Probability x Block:  $F(14,182) = 2.14, p = .012$ , indicating that the extent of learning (i.e. difference between improbable and probable trials) differed significantly between medication state and across blocks. There was also a trend towards significance in the interaction between Probability x Block:  $F(14,182) = 1.57, p = .09$  None of the other main effects or interactions were significant or showed trends ( $p > .1$ ).



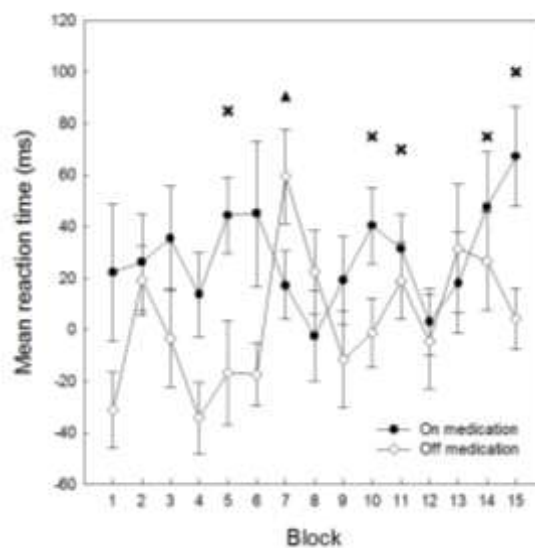
**Figures 5.1a and b:** Mean reaction time for probable and improbable trials, plotted separately for patients on (5.1a) and off (5.1b) medication across 15 blocks of the SRT task. Error bars represent 1 SE.

To clarify the source of the significant 3 way interaction between Medication x Probability x Block, two separate two way ANOVAs were completed with Probability and Block as the within-subject factors, to examine the effects separately on versus off medication. On medication, the main effect of Probability  $F(1,13) = 9.51, p = .009$ , was significant, but the main effect of Block  $F(14,182) = .749, p = .723$ , and the Probability x Block interaction  $F(14,182) = 1.19, p = .284$ , were not. Off medication, the main effect of Probability  $F(1,13)$

= .66,  $p = .433$ ), the main effect of Block  $F(14,182) = .47$ ,  $p = .946$ ), were not significant, but the Probability x Block interaction  $F(14,182) = 2.47$ ,  $p = .003$ ), was significant.

A series of two tailed t-tests were also performed to identify blocks in which learning scores were significantly different On and off medication. (see figure 5.2). Three blocks revealed a difference in learning on versus off medication, where all three were performed better on medication block 4, [ $t(13) = -2.941$ ,  $p = 0.01$ ], block 5, [ $t(13) = -2.313$ ,  $p = 0.04$ ] and block 15, [ $t(13) = -2.392$ ,  $p = 0.03$ ].

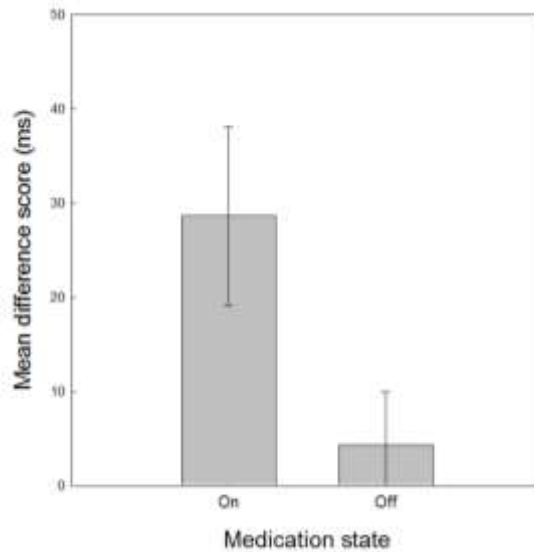
Mean RT difference scores were calculated by subtracting mean RTs for probable trials from those for improbable trials (see figure 5.2). A 2 way ANOVA with Medication (On vs. Off) and Block (1-15) as within subjects factors again revealed a main effect of Medication  $F(1,13) = 6.621$ ,  $p = .023$ ) as well as a Medication x Block interaction  $F(13,182) = 2.120$ ,  $p = .013$ ). These results confirm that learning On medication was greater and that this difference varied across blocks. However, the main effect of Block was not significant ( $p > .05$ ) suggesting that the difference scores did not change across the 15 blocks.



**Figure 5.2.** Mean difference score RTs for patients On and Off medications. The triangle illustrates where mean RTs in each block were significantly different from zero for Off medication and X for On medication respectively. Error bars represent 1 SE.

An ANOVA was also performed on mean difference scores collapsed across all blocks with Medication (On vs. Off) as the within groups factor. The main effect of medication  $F(1,13) = 6.621$ ,  $p = .023$ ), was significant, consistent with previous analysis. Furthermore, t-scores confirmed there was a significant difference in learning between the on and off medication conditions ( $t(13) = 2.573$ ,  $p = .023$ ) (see figure 5.3). The presence of learning was

demonstrated by the difference score being significantly greater than zero, on medication:  $t(14)=3.024, p=.010$ , but not off medication:  $t(13)=.761, p=.460$ ).



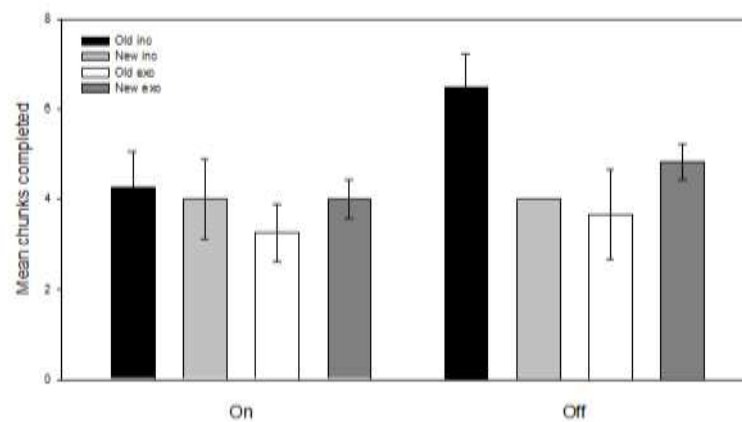
**Figure 5.3.** Mean learning scores collapsed across blocks for both on and off medication. Error bars represent 1 SE.

*Errors:* The same ANOVA was performed as for RT data using mean percent errors for each block. It was expected that if error rates were a reflection of learning, results would demonstrate more errors to improbable trials across blocks whereas errors for probable items should become more infrequent. A 3 way ANOVA was performed using Medication (On vs. Off), Probability (probable vs. improbable trials) and Block (blocks 1-15) as within groups factors and. There were however, no significant main effects or interactions based on error data.

### 5.3.2 Tests of awareness of implicit sequence

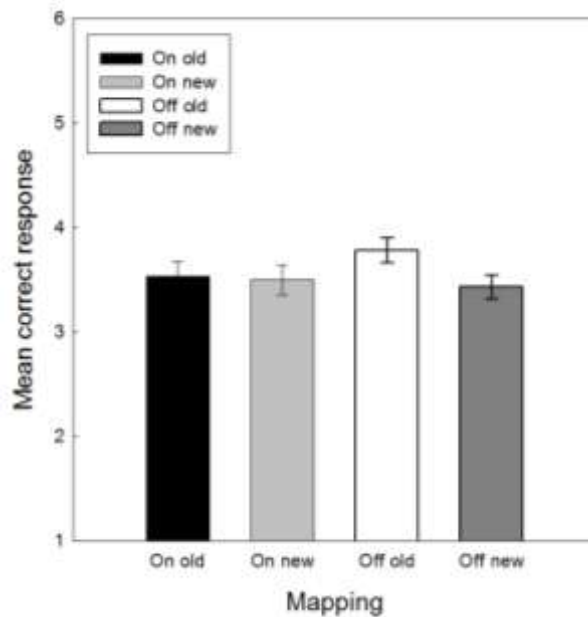
*Process dissociation procedure (PDP).* Finally, the study assessed whether there was any evidence for explicit awareness of the presence of the SOC sequences in either on or off medication conditions. Again, trials were separated so that they were either taken from the probable (learned) SOC or the improbable (unlearned) SOC, or then further divided into inclusion and exclusion conditions (Wilkinson & Jahanshahi, 2007). The last 3 trials of the 6 item chunks were examined and given a score of 1 if they formed a triplet in the associated SOC (see fig. 5.4). The presence of explicit sequence knowledge would be indicated by a significantly greater number of completions for the probable sequences as it is assumed the infrequent presentation of the improbable SOC should result in little, or no, learning.

Figure 5.4 shows the number of old versus new triplet completions collapsed across test order, for both PD patients and controls. For both groups during the inclusion and exclusion tests, and the number of old completions was greater than the number of new completions. The data was analysed using a 3 way ANOVA with Task (Inclusion vs. Exclusion) and Sequence (Old vs. New) and Medication (On vs. Off) as within-subject factors. None of the main or interaction effects were significant. Hence, participants completed a similar number of SOC sequences in both probable and improbable conditions whether or not they were trying to complete the sequence under inclusion or deliberately avoid doing so under exclusion instructions. Therefore, it is concluded that the PDP shows no evidence that participants had developed awareness of the SOC.



**Figure: 5.4.** Mean test chunks completed for both old (Probable) and new (Improbable) sequences. Error bars represent 1 SE.

Finally, the study assessed the performance in the recognition task based on participants' response accuracy and confidence in their judgements. Responses were classified on a six-point scale using the following criteria 1= Sure new, 2= fairly sure new, 3= Guess new, 4= Guess old, 5= Guess old and 6= Guess old. A 3-way ANOVA (with the same factors as the RT data) revealed no significant effects (see figure 5.5).



**Figure 5.5.** Mean recognition ratings for old and new test sequences for On and Off medication conditions. Participants responded to 12 old and 12 new sequences and made a recognition judgment for each sequence (1=certain new, 6=certain old). Error bars represent 1 SE.

#### 5.4. Discussion

Patients with Parkinson's disease exhibited greater sequence learning on a probabilistic SRT task while they were on dopaminergic medication relative to off medication. This difference seems to be particularly pronounced during the first half of the task. Both of these findings were, in part, attributable to a marked attenuation of learning in the off-medication condition. Crucially, there was no evidence for a generalised difference in reaction times between the medication conditions, which makes it unlikely they are explicable as a result of simple motoric difficulties when off-medication. Furthermore, there was no evidence for performance improvements based simply on practice or task familiarity effects (as indicated by the absence of main effects of block and order conditions). As a consequence, the results indicate that the administration of levodopa to PD patients can, at least in part, ameliorate deficits in implicit learning that result from the disease.

These findings add to mounting evidence regarding importance of dopamine during sequence learning tasks, such as the SRT (Badgaiyan et al., 2007; Carbon et al., 2004; Jackson et al., 1995). The current study extends earlier results by demonstrating that considerable attenuation, but not complete abolition, of PD patients' ability to perform such tasks occurs as a consequence of the disease. Importantly, it suggests that tasks of this nature are highly dependent upon brain regions where dopamine is depleted and where dopamine levels are, at least in part, normalised by the administration of levodopa. In general, the



degeneration of dopamine production in PD follows a distinctive spatial-temporal gradient with the greatest loss of DA neurons in early stages occurring in the lateral ventral tier of substantia nigra pars compacta (SNpc), which predominantly project to dorsal striatal areas (Cools, 2006; Fearnley & Lees, 1991; Kish, Shannak, & Hornykiewicz, 1988). There is also considerable depletion of dopamine in the cortical areas to which the dorsal striatum principally projects including the motor cortex (primary (M1), premotor and SMA and the DLPFC. In contrast, dopamine production in the dorsal midbrain is substantially less effected by PD. As a consequence activity is relatively preserved in ventral striatal areas and the cortical areas with which it is heavily interconnected (i.e. the amygdala, anterior cingulate, inferior temporal cortex and the orbitofrontal cortex [OFC]. The absence of any indications of any awareness would question the generality of the hypothesis that incidental learning is critically dependent upon ventral striatal areas and that administration of dopamine will impair performance upon such tasks (Macdonald & Monchi, 2011).

However, applying this understanding of the patho-physiological progression of PD to explain variations in the cognitive affects of levodopa remains a topic of considerable debate. One proposal, first advanced by Gotham and colleagues (1986; 1988), is that the dose of levodopa necessary to ameliorate motor deficits by normalising dopamine levels in areas severely depleted by the disease may result in an ‘overdose’ in less affected areas, such as the PFC. This influential hypothesis has been further developed by several researchers, but of particular relevance to the current study are recent theories that propose differential effects of medication within the dorsal (improved by l-Dopa administration) or ventral striatum (impaired by l-Dopa) may have specific implications for learning (Cools, 2006; Macdonald & Monchi, 2011; Redgrave et al., 2010). In general, these studies indicate that learning tasks in which participants are explicitly aware of their goals and the outcome of their actions is dependent on ventral striatal activity, e.g. probabilistic reversal learning (Cools et al., 2001) and explicit motor sequence learning (Kwak et al., 2010). Furthermore, there is a considerable body of evidence, drawing especially upon animal models, indicating that the ability to acquire and retrieve habitual actions is dependent upon stimulus-response circuits instantiated by the dorsal striatal function (see Redgrave et al., 2010 for a recent review relevant to PD). In general, however, these hypotheses would predict that the expression of habitual action would be impaired when patients are off-medication and improved by the administration of levodopa, and either no effect or even the opposite pattern of results for tasks that involve goal-directed learning.

These predictions are consistent with the considerably greater impairment in learning demonstrated by patients when tested off compared on medication. In the probabilistic SRT

task the study employed participants who were unaware that they were performing a learning task and so learning occurred incidentally whilst performing the primary goal-directed task (i.e. responding as rapidly as possible to a spatially congruent target). As a consequence, sequence learning in the current task is likely to reflect an incremental strengthening of repeated stimulus-response associations (e.g. habit formation circuitry in the dorsal striatum and associated cortical areas) rather than depend on processes and circuits associated with action-outcome evaluation (i.e. the cortico-striatal circuits associated with the ventral striatum). Furthermore, the results may have important implications regarding the action of oral administration of levodopa on tonic dopamine levels and phasic dopamine release, which remains a topic of considerable controversy. Some theorists have contended that dopamine only increases tonic dopamine levels, and that this effect might even serve to mask the effects of phasic signalling (Carbon et al., 2003). One way to potentially resolve these suggestions is to examine the effects of levodopa on tasks thought to tap these dopaminergic systems. Crucially, from the perspective of the current results it has been proposed that phasic release of nigro-striatal dopamine is critical for reinforcing the slow incremental learning that characterises habitual learning in SRT tasks (Wilkinson & Jahanshahi, 2007). As a consequence, the improvements in patients learning on medication observed could indicate that oral administration of l-Dopa facilitates phasic dopamine signalling.

Though this view has been challenged in a recent theoretical model proposed by MacDonald and Monchi (2011), which claims PD patients on dopamine medication are more impaired in implicit learning tasks (i.e. in the absence of any awareness of learning) than when off medication. The authors claim that such tasks are dependent upon the ventral striatum, which is relatively spared in early PD and so in accordance with the dopamine overdose hypothesis adversely affected when patients are on medication. However, it is worth noting that motor sequence learning tasks involve a variety of cognitive processes (e.g. response selection, explicit and implicit retrieval, visuo-spatial processing and selective attention), which MacDonald and Monchi attributed to the recruitment of the dorsal striatum.

The magnitude of learning was far greater for patients when they were on medication than off their medication. Furthermore, this difference between the groups was especially evident in the early blocks of learning, which indicates a more rapid progression of learning when on medication. However, there is evidence that learning was generally more robust (i.e. significantly above zero) for the on medication group in the second half of the training blocks, while only a single block was significantly above chance when patients were off medication. The development of greater learning in the medicated group during later stages

may be consistent with previous findings that levels of dopamine release in the caudate and putamen are increased during sequence learning (Badgaiyan et al., 2007). Although PD patients suffer from impairment in the specific nuclei responsible for this release, L-dopa medication may sufficiently boost striatal dopamine levels to compensate and maintain learning across blocks. The off medication group, of course, do not benefit from this boost in activation and so do not achieve the same levels of learning throughout. The greater separation of learning between the groups in the early stages may be a feature of those in the off medication group struggling to engage the striatum due to reduced levels of striatal dopamine when off medication. Consequently their patterns of learning are not as strong or as consistent as the medicated group. Due to this, they are not as efficient at learning in the early stages and their improvement is variable, whereas the medicated group begin with a higher magnitude of learning and can maintain enough dopamine release across training to consistently demonstrate learning at end of the 15 blocks. One may speculate that given enough time, participants in the off medication group can reach a level of learning similar to that of the medicated scores. Indeed a previous study focusing on progression of learning in six training sessions over six weeks (one session per week) using the SRT with medicated PD patients discovered that learning can be improved over the first three sessions before it plateaus (Doyon et al., 1997). Alternatively, a group with frontal lobe lesions were able to maintain an improvement across all six sessions. This indicates that improvements in PD are possible but are nevertheless limited to the integrity of the striatum.

Participants' lack of awareness that they were performing a sequence learning task was evident in their inability to demonstrate any evidence of explicit knowledge of the sequence structure despite extensive testing. This result is consistent with previous studies of probabilistic sequence learning in PD that also failed to find evidence of awareness of the sequence (Wilkinson & Jahanshahi, 2007; Wilkinson et al., 2009). Importantly, task awareness might also account for differences between the current study and previous studies of motor sequence learning in which participants were aware they were supposed to learn a sequence. For example, a series of studies have investigated the impact of levodopa infusion (Carbon et al., 2003; Feigin et al., 2003; Ghilardi et al., 2007) upon sequence learning with a reaching paradigm in which a cursor is moved to a sequence of 8 target locations using a computer tablet. Results indicate that learning of the target sequences during testing was no different for the on vs. off medication conditions, but that declarative knowledge was greater in the absence of dopamine infusion (Feigin et al., 2003; Ghilardi et al., 2007). These results were consistent with a processing drawing upon less impaired ventral striatal networks associated with action evaluation and goal-directed behaviour. As a consequence, unlike the

current results learning was unimpaired off-medication and participants had some degree of awareness of the sequence. Interestingly, they also report increased activity in the right premotor cortex (part of the dorsal striatal network) during dopamine infusion compared to a non-infusion baseline. Similarly, the importance of the participant's knowledge of whether they are performing a learning task could also account for the apparent contradictions between these results and those predicted by the recent theoretical proposal of MacDonald and Monchi (2011). They argue that both implicit and explicit learning are critically dependent upon the ventral striatum. However, much of their evidence for ventral striatum activity during implicit learning is drawn from tasks where participants are aware of the nature of the task but cannot explain the basis of their learned performance, e.g. the weather prediction task (Wilkinson et al., 2011). In such circumstances it is likely that participants will still engage mechanisms for goal directed learning even if they do not become explicitly aware of the underlying nature of the rule or pattern learned. Overall, these results indicate that some caution should be used when classifying tasks on a simple taxonomy (e.g. implicit/explicit learning) and that other potential taxonomies should be considered (e.g. incidental/intentional learning).

However, it should be noted that explanations of the current results based upon the effects of the disease and medication on the dorsal striatum may result from their contribution to functional networks with other brain areas. Significantly, the dorsal striatum projects to a variety of cortical areas (M1, SMA and PFC) associated with motor sequence learning in functional imaging studies (Toni, Krams, Turner, & Passingham, 1998). A recent study Badgaiyan et al., (2007) examined dopamine levels in the striatum during an SRT task by using PET to measure changes in the concentration of  $^{11}\text{C}$ -raclopride. They found maximal activation during learning in the dorso-posterior putamen, which is heavily interconnected with primary and supplementary motor areas (Badgaiyan et al., 2007). Similar, reduced activity in the putamen was also reported by Goerendt and colleagues (2003) in a PET  $^{11}\text{C}$ -raclopride study comparing PD patients and controls during a sequential finger movement task (Goerendt, 2003). Finally, a recent study using a rodent model demonstrated that lesions of the ventral tegmental area (VTA) reduced dopamine enervation to M1 and impaired sequence learning, which were both ameliorated by the infusion of levodopa (Hosp, Pekanovic, Rioult-Pedotti, & Luft, 2011). Initially, this may seem contradictory because as noted above VTA is largely unimpaired in PD and project to the ventral striatum, but as M1 also receives projections from the dorsal striatum it may be sensitive to its impairment. This may suggest that some caution is required in interpreting the effects on complex cognitive tasks based on division of dorsal and ventral striatum. The findings of these studies as well

as the ones presented in this chapter would seem to suggest that striatal dopamine can not only systematically improves working memory functions as mediated by the dorsal caudate (Sawamoto et al., 2008 also see section 5.1.) but also modulates the putamen during sequence learning. For this reason, l-Dopa prescribed medication may improve performance on these tasks in PD.

In conclusion, the study discovered that levodopa medication enhanced performance of patients with PD on a probabilistic sequence learning paradigm. It is possible, that the motoric component of the response selection in the SRT engages an associative circuitry which is dependent on medication. As has been discussed, learning of an implicit task can involve a far more complex series of activations than previously assumed, based on goal directed performance of the motor execution as well as unconscious learning of a sequence. Consequently, sequence learning tasks can engage a range of activity combining motor and cognitive processing that in this case depend heavily on the basal ganglia and in particular areas mediated by levodopa medication. This effect may have been achieved through the use of probabilistic sequences and the complexity of the sequence structure maintaining implicit performance. Appreciating the significant impact of subtle methodological differences may be one step towards understanding the defining impact of levodopa medication on cognitive processing. Another, crucial aspect is that of contributing regions and circuits that project to and from the striatum and their concurrent impact on overall task performance in response to levodopa medication. Again it is possible that projections from external sources are benefiting from an levodopa enhanced dorsal striatum and better equipping what may be considered as secondary processing regions such as M1 to contribute to learning.

## Chapter 6

### VI. Impact of Deep Brain Stimulation on probabilistic sequence learning in Dystonia

#### 6.1. Introduction

Deep Brain Stimulation (DBS) is becoming increasingly widespread as a treatment for a range of neurological illnesses. The procedure involves bilateral or unilateral insertion of an electrode in areas of the brain that are thought to be responsible for the treated symptom. Once inserted, the electrodes are activated to either stimulate or inhibit (depending on the stimulation parameters) neurone's in that area. However, the cognitive effects of stereotactic lesions that interact with pathways of the Basal Ganglia (BG) and their projections to the frontal lobe remain unclear. In part, this is due to conflicting findings of studies investigating DBS of the Subthalamic Nucleus (STN) and the internal segment of the Globus Pallidus (GPi) in diseases such as Parkinson's and dystonia (Carbon et al., 2003; Fukuda et al., 2001; Tisch et al., 2007) though the general conclusion is that cognitive modulation is possible when the electrodes are active (Stamelou, Edwards, Hallett, & Bhatia, 2012).

Dystonia is a movement disorder characterised by structural impairments in the BG resulting in twisting and locking of limbs (Grafman, Cohen, & Hallett, 1991). Similar to Huntington's disease, dystonia can include genetic markers that can be screened for, although not all carriers of the DYT1 mutation will contract the disease (Hallett & Pisani, 2011). Of these patients, there are two important distinctions based on whether they have primary/idiopathic or secondary dystonia (Zoons, Booij, Nederveen, Dijk, & Tijssen, 2011). While primary dystonia is largely free of any noticeable brain abnormalities, patients with secondary dystonia can have lesions in the basal ganglia (Zoons et al., 2011). There are several possible manifestations of dystonia, such as focal (which can affect any specific part of the body i.e. focal hand) or generalized forms which can include the legs and neck. Typically, dystonia will be contracted at an early age (in teenage years or twenties) (Hallett & Pisani, 2011). Imaging studies have discovered abnormalities in the basal ganglia, cerebellum and SMA in focal dystonia (see Zoons et al., 2011 for a review) and disturbances to the globus pallidus in primary dystonia (Berardelli et al., 1998).

Thus far, reports published regarding improvements to motor functions after DBS for primary generalized dystonia have been largely favourable (Vidailhet et al., 2005). In most cases, electrodes are inserted in the GPi where studies have demonstrated abnormal activity (Vitek et al., 1999). Activation of these electrodes are known to illicit activity in the GPi at

resting state (Detante et al., 2004) but to inhibit it and other (prefrontal) areas during movements (see Berardelli et al., 1998 for review).

In comparison to other movement disorders there has been little research conducted on patients with dystonia, but the disease is generally thought to have very little effect on cognitive function (Jahanshahi et al., 2001). Nevertheless, research is now beginning to focus on the cognitive aspects of the disease (see Stamelou et al., 2012 for a review). Some studies report that, in comparison to controls, patients with dystonia have impaired extra dimensional set-shifting (Balas, Peretz, Badarny, Scott, & Giladi, 2006) and are more susceptible to retroactive interference in verbal memory (Scott et al., 2003). Additionally, it has also been reported that patients can outperform healthy controls on verbal fluency tasks (Balas et al., 2006). Nonetheless, due to the relative sparing of their cognitive abilities, dystonia represent an intriguing population for studying the effects of DBS, as any consequence of performance after surgery would directly implicate the procedure as opposed to neurological degradation from disease pathology.

Recently published investigations of the impact of DBS in Dystonia have concluded that such interventions do not alter performance on a range of cognitive tasks (Gruber et al., 2009; Pillon et al., 2006; Vidailhet et al., 2007) but others claim that it can improve executive functions (Halbig et al., 2005; Pillon et al., 2006). More directly related to the present study, recordings of GPi activity with and without stimulation suggest that DBS may benefit motor specific movements whilst suppressing activity in frontal areas such as the DLPFC (Detante et al., 2004) known to be involved in sequence learning. Subsequently, DBS of the GPi may happen to improve cognitive tasks dependent on motor movements such as the SRT.

Electrophysiological studies have identified abnormal levels of activity in the Globus Pallidum as a route cause of motor deficits in dystonia (Gernert, Bennay, Fedrowitz, Rehders, & Richter, 2002; Vitek, 2002), and so it is the target for DBS treatment of the disease. Studies of GPi stimulation in Parkinson's disease suggest that it may affect fronto-striatal and cortico-striato-pallido-thalamo-cortical loops (Fukuda et al., 2002) As these networks have been consistently demonstrated to be active in sequence learning experiments (Feigin et al., 2003) it is possible that modulation of the GPi, may alter this process (Ghilardi et al., 2003). Further support for this contention is provided by Brown and colleagues (2003) who reported that surgical lesions to the globus pallidus in PD patients eliminated incidental learning relative both to controls and un-operated patients. These impairments were argued to result from the lesions affect on connectivity with the striatum, which is generally thought

to be responsible for the impaired acquisition of habitual processing of implicit information in PD (Kelly et al., 2004; Knowlton et al., 1996; Reiss et al., 2005; Wilkinson & Jahanshahi, 2007). The key to this form of implicit processing is that any learning of the sequence is developed incidentally, restricting activity in the medial temporal lobe where explicit representations are facilitated (Poldrack, Prabhakaran, Seger, & Gabriel, 1999).

Although, several studies have examined sequence learning in patients with dystonia and carriers of the DYT1 mutation they largely focus upon intentional paradigms where participants are aware they are performing a learning task. An early study by Grafman and colleagues (1991) reported no difference between dystonia patients and controls in sequence learning. However, this has been challenged by results of intentional trial and error learning paradigms (Carbon et al., 2008, 2011; Ghilardi et al., 2003), which indicate carriers of the DYT1 gene who have non-manifested dystonia show impaired sequence learning in comparison to controls but no motor control problems. This impairment has also been replicated in animal studies, where it has been reported that mice infected with the DYT1 gene have been unable to learn sequential information (Sharma et al., 2005). Nonetheless, there are important limitations to these studies. First, learning in the tasks is intentional and so results in goal directed behaviour that may be more specifically related to frontal and temporal areas. Greater impairments are likely in incidental learning that seem especially reliant upon the BG and striatum (Doya, 2000; Wilkinson et al., 2009). Second, the tasks they use measure learning through a random block taken at a single point in time towards the end of training, which as was noted earlier (see chapter 3) can interact with motoric factors to distort results and does not allow measurement of the development of learning.

The current study examines the impact of DBS of the GPi in patients with dystonia in order to identify its impact on a task designed to measure incidental sequence learning, the SRT. Importantly, whilst the precise mechanisms underlying information processing in the SRT are subject to debate it is believed that learning takes place on the basis of fronto-striatal connections that break down the combined motoric and perceptual features of the task (Hazeltine et al., 1997; Rauch et al., 1997; Rauch et al., 1995). Imaging studies using the Serial Reaction Time (SRT) task have consistently provided support for the role of the striatum in the SRT by demonstrating activity in the putamen and caudate (Rauch et al., 1997). However, there is debate as to whether incidental tasks such as the SRT can be successfully performed in the absence of striatal activity (Rauch et al., 1997) as appears to happen for intentional learning tasks in this patient group. Furthermore, considering the evidence for GPi involvement in these tasks and the suggestions that its stimulation regulates firing activity in the basal ganglia and frontal areas, there is reason to believe that



performance may be modulated in these patients. Results are presented for two studies, (i) a within groups design in which the same patients were tested pre and post operatively and (ii) a between groups design in which post operative patients were compared to matched controls who had not undergone surgery.

## **6.2. Methods**

### **6.2.1 Participants**

Thirteen participants with idiopathic Dystonia were tested pre- (Mean age 43.6 SD =16.7) and post-operatively (Mean age 46.3 SD =15.8). Participants were also screened for cognitive impairment, using the Mini Mental State Examination [MMSE] (29.3 SD= .72), and depression, with the Beck Depression Inventory [BDI] (9, SD= 5.6). Furthermore, a group of age matched healthy controls were also tested (n=13) (Mean age 55.1 SD =10.1). All control participants (Time1 Mean age 55.9 SD =10.2, Time2 Mean age 55.1 SD =10.4) performed the task twice, similar to Dystonia patients.

Separates group of un-operated (n=9) (Mean age 40.7, SD =19.7) and operated (DBS) (n=9) (Mean age 47.2, SD =21.6) patients with Dystonia were each tested once. Participants were also screened for dementia, using the MMSE (29.4, SD= .75), and depression, with the BDI (6.5, SD= 5.9). These participants were matched with a healthy control group (n=14) (Mean age 55.9, SD =10.2).

All patients were recruited from the National Hospital for Neurology and Neurosurgery and the study was approved by The National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee. Informed consent was taken from all individuals prior to participation.

### **6.2.2 Materials**

Participants were tested on a Dell insperon 17inch laptop with a LCD display monitor. Responses were made on the button box.

### **6.2.3 Design and Procedure**

Participants in the within groups study performed the task on two occasions (before and after surgery for the patients), and those in the between groups study once. Participants were instructed to place four fingers from their dominant hand (index, middle, ring and little finger) over the four corresponding buttons. They are informed that they will see four white

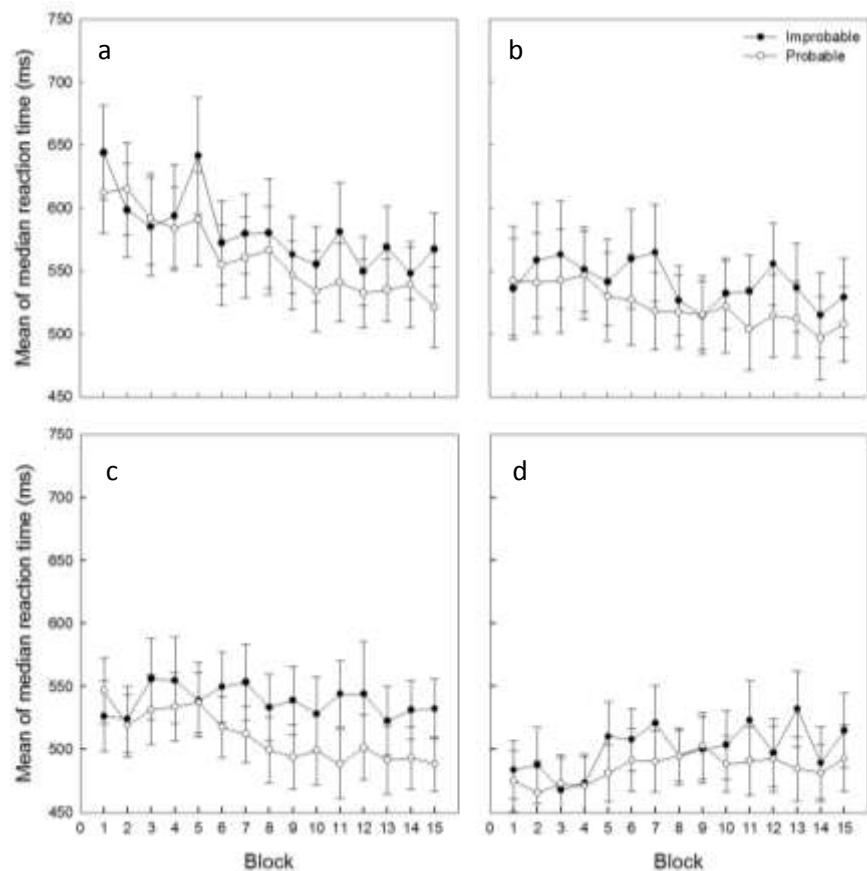
boxes appearing on a grey background with an “x” symbol appearing in any one box at a time and that time they see the symbol they are required to press the appropriate button with a logical sequence to response mapping (see fig. 2.1). The symbol remained on the screen until a button is pressed, at which point the symbol moved to the next location for a correct response. In the event of an incorrect response, a tone was sounded and the symbol remained in the same location until the correct button is pressed. Reaction times were measured from the moment a trial is presented to the instance a participant provides a correct response. Errors were also recorded for each incorrect response and labelled as such. The task consisted of 15 blocks of 100 trials with each key press denoting a trial. Participants are instructed to respond as quickly and as accurately as possible while performing the task, and are permitted to take a short break between blocks if required.

#### **6.2.4 Data presentation**

All reaction times over 2.5 standard deviations from each participant’s overall mean RTs were excluded (2.3%). These were considered to be outliers caused by momentary lapses of concentration and therefore removed as inaccurate readings. Consistent with previous studies (See Wilkinson & Jahanshahi, 2007) analysed RTs were comprised of both correct and incorrect responses. This makes allowance for the likelihood that a considerable number of patient errors, especially when off-medication, are likely to result from simple difficulties in kinetic control (i.e. multiple fingers are engaged per trial) rather than incorrect response selection. Median RTs for participants were collapsed across trials. Scores were converted into difference scores (Wilkinson & Jahanshahi, 2007) where improbable trials are subtracted from probable trials. This provides an overall measure of learning which can be collapsed across blocks.

## 6.3. Results

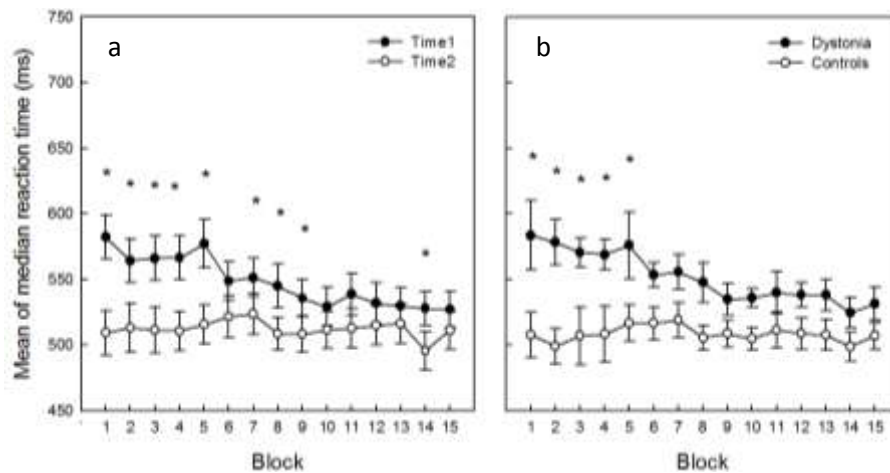
### 6.3.1 Within groups comparison



**Figure 6.1:** Mean of median reaction time for probable and improbable trials, plotted separately for patients before (a) and after (b) surgery and healthy controls at time 1 (c) and 2 (d) across 15 blocks of the SRT task. Error bars represent 1SE.

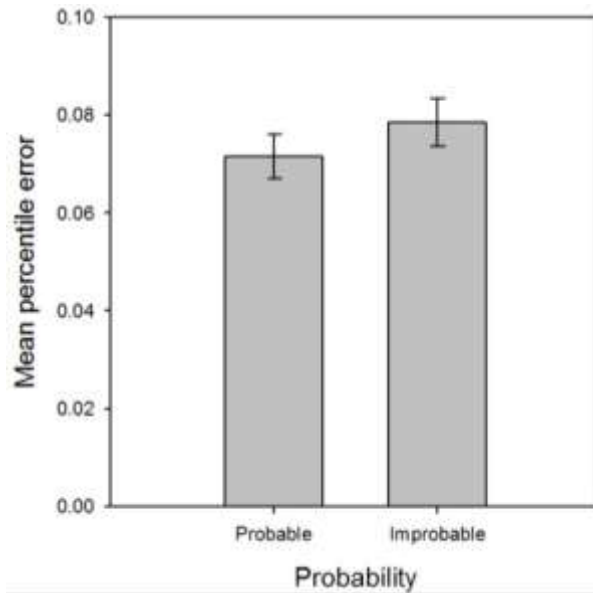
Figure 6.1 depicts the median RTs in probable and improbable conditions for patients (a and b) and controls (c and d). Results are shown separately for both testing times, which were before and after surgery for patients. A 4-way ANOVA was performed on the median RTs with Time (time 1 vs. time 2), Probability (Probable vs. Improbable) and Block (1-15) as within subjects factors and Group (Dystonia vs. Controls) as a between groups factor. The main effect of Probability ( $F(1,24)=24.712, p<.001$ ) indicated that learning had taken place (see fig. 6.1). Participants tended to respond faster to the stimuli in later blocks (Block:  $F(1,14)=3.78, p<.001$ ). Both participants groups performed the task faster the second time (Time:  $F(1,24)=9.07, p=.006$ ) (see fig. 6.2a). There was little discernible difference in the magnitude of learning for both dystonia patients and controls (Group x Probability interaction;  $F(1,24)=.074, p=.787$ ). The degree of learning (improbable minus probable RT) was different across the 15 blocks (Probability x Block:  $F(1,14)=2.290, p=.005$ ). Changes in

RTs for control participants across blocks were much smaller than for patients with dystonia who became considerably faster (Group x Block:  $F(1,14)=3.125, p<.001$ ) (see fig. 6.2b). RTs for both groups became much faster over the 15 test blocks at time 1 (Time x Block:  $F(1,14)=3.026, p<.001$ ) (see fig. 6.2a). There was also a trend towards significance in the Group x Time x Probability x Block ( $F(1,24)=1.666, p=.061$ ) interaction. No other effects were significant or showed a trend.



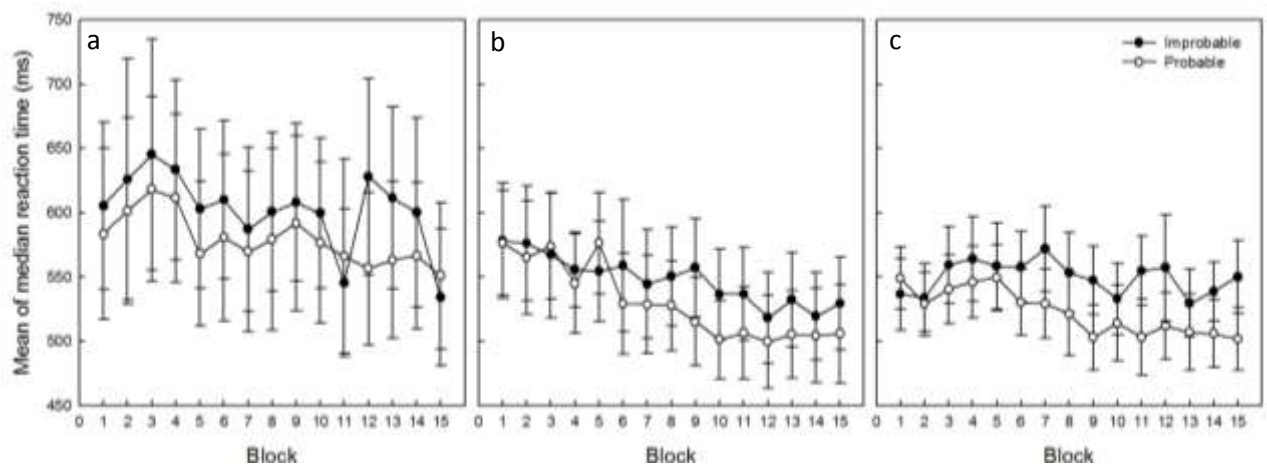
**Figures 6.2.** Mean of median RTs in all 15 blocks for all participants a) collapsed across time and probability plotted separately for testing time and block (stars depict significantly different blocks) and b) collapsed across group probability and testing time (stars depict significantly different blocks). Error bars represent 1 SE.

*Errors:* The same 4 way ANOVA as for RT data was performed using median percentile errors for each block. To do so the number of probable and improbable trials in each block were identified and the percentile error rate for each was calculated. It was expected that if error rates were a reflection of learning, results would identify more errors to improbable trials across blocks whereas errors for probable items should become more infrequent. Participants made fewer errors in the probable condition (Probability:  $F(1,22)=17.059, p<.01$ ) (see fig. 6.3). There was a trend for the control group to make fewer errors than patients (Groups:  $F(1,22)=3.647, p=.069$ ). All remaining main effects and interactions were not significant.



**Figure 6.3.** Median percentile errors for probable and improbable trials, collapsed across all 15 blocks for dystonia and healthy controls. Error bars represent standard error. Error bars represent 1 SE.

### 6.3.2 Between groups comparison

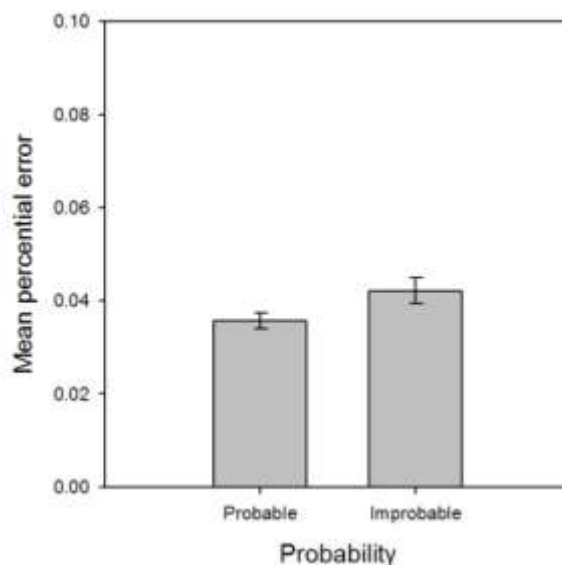


**Figures 6.4. a, b and c:** Median reaction time for probable and improbable trials, plotted separately for unoperated (9a) and operated (9b) Dystonia patients as well as controls (9c) across 15 blocks of the SRT task. Error bars represent 1 SE.

Figure 6.4 depicts the median RTs in probable and improbable conditions for patients without a DBS stimulator (fig. 6.4a), patients with a stimulator (fig. 6.4b) and controls (fig. 6.4c). A 3 way ANOVA was performed on median RTs with Probability (probable vs. improbable trials) and Block (blocks 1-15) as within subjects factors and Group (operated Dystonia vs. un-operated Dystonia vs. Controls) as a between groups factor. Again learning was present (Probability: ( $F(1,29)=21.510, p<.001$ ), and at a very similar level across all three groups (Group x Probability: ( $F(2,29)=.377, p=.689$ ). In general, RTs improved across

all 15 blocks (Block: ( $F(5.224,151.482)=3.408$ ,  $p=.005$ ). No other effects or interactions were significant or showed a trend.

*Errors:* The same ANOVA on errors with Probability (median percentage error for probable and improbable trials) and Block (blocks 1-15) as within factors and Group (Dystonia un-operated vs. dystonia operated vs. Control) as a between groups factor were performed. The main effect of Probability ( $F(1,29)=32.163$ ,  $p<.01$ ), was significant, meaning that participants performed fewer errors in the probable condition (see fig. 6.5). However, all remaining interactions were not significant.



**Figure 6.5.** Median percentile errors for probable and improbable trials, collapsed across all 15 blocks for dystonia and healthy controls. Error bars represent 1 SE.

#### 6.4 Discussion

Results from two studies indicate that despite their neurological impairment participants with Dystonia can learn a complex sequence of locations, without being told of its presence, as well as age-matched controls. Furthermore, there was no evidence that patients' ability to learn was modulated by DBS of the GPi. The result contrasts with those for patients with Parkinson's disease who demonstrate attenuated incidental learning of motor sequences in the current paradigm, which is thought to be a consequence due striatal dysfunction (Wilkinson & Jahanshahi, 2007; See also chapter 5). However, the results appear to be slightly at odds with recent studies indicating that the fronto-striatal circuitry is damaged (Jahanshahi et al., 2001).

There are several possible interpretations of the lack impairment on or off DBS stimulation in dystonia. First, structural deficits, causing a dopamine imbalance in dystonia may not be

sufficiently severe, or critically localised, to impair performance on the SRT. Second, DBS stimulation of the GPi may simply not affect incidental sequence learning. Although, some executive tasks are known to be affected by this type of stimulation many others are unaffected. Therefore, it is possible that remote effects on striatal projections to the frontal lobes, which are thought to underlie the executive deficits, were insufficient to cause any impairment in this particular task. Thirdly, patients with dystonia may have adapted to use a different network of brain areas to perform incidental learning tasks, and so their learning would be less susceptible to basal ganglia and fronto-striatal impairment than other clinical groups.

The latter proposal draws upon findings in intentional motor sequence learning for DYT1 gene carriers who have not manifested dystonic symptoms (nmDYT1), who despite showing no deficits in motor task performance are nonetheless impaired in sequence learning (Carbon et al., 2008, 2011; Ghilardi et al., 2003). Ghilardi and colleagues (2003) used PET to identify differences in the networks of brain areas recruited during these tasks by nmDYT1 and matched control participants. Despite the absence of motor performance deficits they found abnormally high levels of activity in the left prefrontal cortex, right SMA and cerebellum during execution of movements. Importantly, during sequence learning they found substantially increased activity in the lateral cerebellum. A similar result was reported by Carbon and colleagues (2008) within a trial and error motor learning paradigm. They found that nmDYT1 participants showed significantly less activity bilaterally in the DLPFC, the left anterior cingulate and the left dorsal premotor cortex. However, they showed far greater activation of the lateral cerebellum, which was only apparent in controls at high levels of task difficulty and so the authors propose that it was recruited as a compensatory mechanism. These differences in activity raise the question about whether they reflect a cortical reorganisation to compensate for acquired deficits in processing in striatal areas or if a fundamental organisational difference occurring from an early age. The latter would potentially predict very different effects in this group from other patients who acquire deficits as it suggests that their learning networks may have never been organised in a typical normal participants.

Together, these studies seem to produce a compelling picture of cerebral activation during intentional sequence learning in dystonia. However, it is less clear whether such activation is also likely to occur during incidental sequence learning, especially when specified in a probabilistic paradigm. The cerebellum is generally considered to be involved in the incremental optimisation of motor skills (Kitazawa et al., 1998). For example, it is known to be critical for motor adaptation to prism induced visual displacement (Martin, Keating,

Goodkin, Bastian, & Thach, 1996). However, it is possible that a paradigm that cannot be completed by simple repetition of motor sequences or reinforcement of the current visuo-motor association might benefit less. However, recent theories have argued that it also has important cognitive functions, especially within associative learning and working memory (Bellebaum, Daum, & Suchan, 2012). Thus, a potential role in incidental motor sequence learning is at least plausible. On a purely behavioural level the current results suggest that any reorganisation occurring of processing occurring incidental learning is more effective than that for intentional learning as patients show no deficits in the task in contrast to the findings for nmDYT1 carriers. Furthermore, it might be expected that patients show more extreme affects than asymptomatic gene carriers. However, some caution is required as the current study involved a clinically manifested patient cohort including both DYT1 positive and negative gene participants. Carbon and colleagues (2011) recent findings that intentional sequence learning in nmDYT6 participants was not impaired. Thus, more work is required investigating the patterns of deficits in different sub-groups that both do and do not manifest symptoms.

Finally, a consideration is required for the heterogeneity of the sample. As mentioned there are many forms of dystonia and further implications for brain abnormalities based on whether they have primary or secondary dystonia. Furthermore, there are different gene states which as discovered by Carbon and colleagues (2011) can have a bearing on performance. Furthermore, it has been suggested that the reported variable in the degree of benefit to motor functions as a result of DBS may be a feature of the heterogenic samples involved in studies (Vidailhet et al., 2005). The authors also report that patients in their sample of dystonia with phasic movements responded better to DBS than those with tonic movements (Vidailhet et al., 2005). Consequently, the results obtained in this study may be subject to the same effects where patients from certain gene types who are not cognitively affected by DBS are diluting the results of other patients who perhaps are. Further studies should therefore, recruit from homogenous samples of dystonia to investigate whether there are indeed, some forms of the disease that respond differently to treatment.

In conclusion, the results demonstrate that dystonia patients with and without GPi stimulation are unimpaired on an incidental sequence learning task presented probabilistically, which contrasts with the presence of deficits in this particular task in PD patients and deficits in intentional sequence learning in dystonia. It is unclear whether the results reflect a differential neural basis for learning within such tasks in dystonics, or simply a greater preservation of critical areas in this disease, which are also less effected by stimulation. However, the performance of incidental learning tasks by dystonics would



benefit from imaging studies to clarify their neural mechanisms, and cognitive effects of GPi stimulation also remains an open question.

## Chapter 7

### VII. General discussion and evaluation of studies

#### 7.1. General Discussion

The thesis has attempted to draw together diverse elements of experimental and cognitive psychology with findings on the neuropsychological aspects of learning in order to demonstrate the importance of maintaining an eclectic approach to how we investigate sequence learning. Considering the complex processes that are involved in sequence learning, it is important to maintain an appreciation for the differences that exist between the intentional and incidental literature as well as those between the SRT and other paradigms.

##### 7.1.1 Study 1: Compatible vs. incompatibility in incidental learning

The first study consisted of two experiments investigating fundamental aspects of learning concerned with how learning is measured and how this can be a determining factor on the results obtained. Spatial congruity between stimuli and response mappings is of course a beneficial feature for fast and accurate RTs; however, participants still demonstrate the ability to learn under incompatible spatial mapping conditions despite the additional complexity of the mapping. Paradoxically, despite the additional difficulty of the task a previous study suggested that learning under an S-R mapping can be superior to that of a traditional compatible condition (Deroost & Soetens, 2006b). The first chapter of this thesis has clarified this debate by demonstrating the significance of how learning is measured and the use of repetitive locations and their interaction with RTs in sequence and non-sequence trials. In a first experiment, it was demonstrated that under probabilistic constraints, when learning is measured throughout training and where repetitions are removed, learning of compatible and incompatible conditions are, at best, equal. In a second experiment, adopting a finite state grammar similar to that of Deroost and Soetens (2006), conflicting results were discovered when learning was calculated using RT difference scores comparing sequence trials with non-sequence trials either occurring probabilistically throughout the training period or in a random block late in the training period. In this case, probabilistic assessment revealed no difference in learning between the S-R mapping conditions, whereas random block analysis suggested that participants in the incompatible group learnt better. It seems likely that the defining feature of the learning outcome depends on the learning metric used. However, the second experiment in chapter 3 has also revealed that repetition in the sequence structure can elicit faster responses most probably due to their reengagement of motor priming which can have proportionately better improvements for incompatible

conditions. These faster RTs are likely to create large discrepancies amongst the dataset and artificially inflate scores, particularly when learning is represented through a random block.

### **7.1.2 Study 2: Perceptual manipulations of incidental sequence learning**

The second study consisted of three experiments focused on another aspect of sequence learning that is still poorly understood, regarding which features of the task can enhance learning. Various studies have investigated learning in the presence of distractors as well as the ability to process a degree of information from a concurrent sequence, even when instructed not to pay attention to it, but few have examined whether concurrent information can enhance learning. The next study focused on the specific features of sequence learning that contribute towards enhancing performance. The investigation employed colour, spatial and perceptual cues to identify their distinct contributions. Sequence learning based on a primary feature of the stimulus was accompanied by non-behaviourally relevant secondary features providing additional information regarding the next item in the sequence. The secondary cue only enhanced performance when both primary and secondary cues were spatial and the secondary cue was presented in blocks. This implies that spatial properties are beneficial when the presentation order has a commonality (such as in the blocked condition where three consecutive transitions would occur on the same horizontal row), indicating that spatial properties can enhance complex sequence learning. It is possible that spatial presentations require fewer demands from working memory in order to identify the chunks of commonalities amongst sequence structures. Blocked formations of spatial presentations may, therefore, present this ordered information in a way that can be meaningful to participants as locations appear on the same row. The mixed condition may not provide any benefit as its changing vertical correspondences require processing of an ever changing spatial environment which is more difficult to be dissociated from random transitions, thus requiring more working memory to identify the horizontal and spatial rule. The blocked condition on the other hand can be chunked into four horizontal sequences in separate vertical locations, which may have been more salient to the participants and encouraged a deliberate strategy of attending in part to the vertical cue. Although the mixed group contains similar FOC properties (i.e. in both conditions the next location is uniquely determined by the current horizontal and vertical location), the large variations in the vertical positions may have been more likely to appear random. A reason for this may be due to participants failing to appreciate what constitutes randomness. It is often thought that random patterns will be reflective of constant changes in the environment whereas, in actual fact similarities in random orders can be just as possible. For example, a transition of 1, 2, 3, 4, is no more random than 3, 1, 4, 2, however, as a pattern of 1-4 has contextual significance (or common

dimensionality), it seems to be ordered as opposed to random. Consequently, people may consider structured, but irregular formations such as 3, 1, 4, 2, to be more random than genuinely random orders (Falk & Konold, 1997; Kunzendorf & Pearson, 1984). It is possible that the blocked condition reinforced these misconceptions about randomness, whereas the mixed condition suffered from these same misunderstandings to suggest to there being no meaningful order. Working memory may have a crucial role in this as learning of these secondary features may be spatially more challenging and overwhelming in the mixed condition, whereas the blocked condition can be more easily chunked based on its common dimensionality and perhaps even based on further strategies that may have encouraged participants to chunk the four horizontal rows as four unique sequences. A similar effect was noticed in the other conditions as coding based on colour or perceptual features alone is not distinctive or meaningful enough to avoid additional working memory processing of the stimuli to allow automatic incidental learning of both the primary and secondary sequences.

### **7.1.3 Study 3: l-Dopa induced modulation of learning based on striatal integrity**

The third study attempted to investigate how sequence learning is affected in patients with PD and the role of l-Dopa medication. Although participants were able to learn the sequence, the study confirmed the hypothesis that patients with PD will perform the task better when they are taking levodopa medication than when they are not. Considering that levodopa medication has often been demonstrated to show the reverse in cognitive tasks, this study is the first to demonstrate this effect using the probabilistic SRT task in PD. Sequence learning research has consistently revealed activity in the striatum (Aizenstein et al., 2004; Berns et al., 1997; Destrebecqz et al., 2005; Doyon et al., 1996; Grafton et al., 1995; Peigneux et al., 2000; S L Rauch et al., 1997; Rieckmann et al., 2010; Schendan et al., 2003) as well as demonstrating the role of dopamine in learning. As explained in chapter 5, some researchers have begun to explore the roles of subdivisions of the striatum (dorsal and ventral) to postulate specific roles for each. One such proposal from McDonald and Monchi, (2011) suggests that l-Dopa should improve the dorsal but impair the ventral striatum due to the former being more seriously affected from innervations from the dopamine depleted VTA and the latter being relatively spared but consequently overdosed by medication. However, this study has reinforced the belief that the dorsal striatum modulates incidental learning and that this can be improved by the administration of l-Dopa medication in PD.

It appears that an important aspect for ones appreciation of learning and how it is interpreted from neurological data is largely dependent on ones understanding of behavioural and cognitive research. Due to this, there is an increasing appreciation for how subtle differences

such as goal directed information can incur confounding implications for degrees of awareness and strategies that take place during these tasks. For instance, McDonald and Monchi (2011) present their paradigm to be an implicit learning task but do not consider the implications for participants being aware of the learning properties that significantly alter the nature of their experiment (see chapter 5). Understanding these principles can be the key to accurately interpreting activation patterns and dissociating information that may seem to be contradictory. Furthermore, the study suggests that we may need to slightly alter our understanding of l-Dopa medication and its role in cognition. Although, the thesis does not contest that the overdose hypothesis is accurate for a wide variety of cognitive tasks, it does propose that it differentially influences performance based on the very specific properties of the paradigm and that this may be dependent on dorsal and ventral processes in PD. Further investigations are required to identify other tasks that may engage the basal ganglia's associative loop in the same way as the SRT to clarify whether these tasks are also benefited by l-Dopa medication in PD.

#### **7.1.4 Study 4: Stimulation of the GPi and its role in incidental sequence learning in dystonia**

The final study sought to eliminate the possibility of general cognitive decline interfering in the accuracy of interpretations from basal ganglia disorder patients by recruiting a population that are thought to have little to no cognitive impairments (dystonia patients). Furthermore, as previous studies have suggested that the GPi may be interacting with learning of sequential information, the study explored a series of patients who were tested before and or after receiving stereotactic lesions (DBS) of the GPi. Results demonstrated that learning was not modulated by DBS, nor were dystonia patients impaired compared to a group of healthy age matched controls. The results are consistent with the view that the striatum is primarily responsible for incidental sequence learning and that the GPi, although part of the basal ganglia network, does not interact with learning. However, based on structural irregularities and the uncertainty of how they affect patients with dystonia, it is difficult to accurately develop this argument. Nevertheless, recent studies have led to the hypothesis that patients with dystonia experience neural plasticity, diverting processing for incidental learning to the cerebellum. As studies have demonstrated that the cerebellum can be associated with some incidental sequence learning experiments, this seems to be a plausible argument. More research is therefore, required to identify whether participants with dystonia are performing the SRT with processing resources from the striatum (indicating that it is intact) or utilising the cerebellum (suggesting that it too is capable of fulfilling incidental sequence learning).

## **7.2. Methodological considerations for sequence learning**

Together, these studies have drawn on behavioural and neurological components of sequence learning and demonstrated the value of both aspects to aid our understanding of cognitive and neural processes. The behavioural aspects that we are aware of have demonstrated that our interpretation of learning must be far more tightly confined to the specific parameters of each experiment than is currently the case. This is particularly necessary when exploring complex (and perhaps poorly understood) aspects such as compatibility, as confounding variables may significantly affect the interpretation of the results (as discussed in chapter 3). Although this thesis does not reject the general results demonstrated by Deroost and Soetens (2006), it does recommend that learning in this task is not indicative of learning in other similar experiments. A significant feature of Deroost and Soeten's (2006) design was to incorporate repetitions of locations into their experiment. They argue that as these repetitions are controlled for in the random block, they should be considered to be equally accounted for in both compatible and incompatible variations. However, the authors may well have overlooked a crucial interaction between responses to repetitions for compatible vs. Incompatible mappings. The findings in this thesis would suggest that these RTs to repetitions are disproportionately faster in the incompatible condition than they are to non-repeating transitions, regardless of whether the repetition is part of the probable or improbable sequence rule. Due to this, matching the number of repetitions present in a random block does not satisfy the problematic influence that they have on RTs, as incompatible trials are differentially effected to compatible ones. Indeed, two previous studies had directly explored the effect of repetitions in sequence learning and both had concluded that RTs to these items are disproportionately faster to other trials and that this effect is not reflective of learning (Bertelson, 1961; Hyman, 1953). It is unfortunate that these basic principles of the impact of sequential information in early studies are much forgotten and unconsidered in more recent times. However, the results of the second experiment in chapter 2 demonstrate that the use of repetitions is an aspect that should be given more consideration and support the reservations first raised by Hymans (1953) and Bertelson (1961).

Further reservations regarding methodological aspects of sequence learning that may have been taken for granted have been developed by a group suggesting that variability based on SOC sequences can also influence results (Kemény & Lukács, 2011). Kemeny and Lukacs measured learning obtained from a group of participants who all trained on the same SOC sequence against that of a separate group who all performed a different set of SOC sequences. The authors discovered that although the conditions were identical in every way

other than the fact that one involved the same SOC for each participant and the other used different SOCs, learning was significantly greater for those in the same SOC condition. The authors argue that future experiments should use different SOC sequences in order to avoid generalised results based on specific features of any one SOC as one may potentially be easier or harder to learn than others. It can be argued that Deroost and Soetens (2006) may be subject to this effect as all their participants performed the same grammar and were all therefore subject to the same potential biases in response transitions. However, the studies conducted in this thesis generally used four different SOC formations for its initial probabilistic SRT experiment. It can be argued that these studies are far less likely to be subject to these potential confounds.

Methodological procedures are becoming ever more important to examine as modern day investigations of sequence learning are becoming more advanced and more ambitious in their pursuits. As well as the issue of learning metrics and repeating locations, perhaps it is also important to consider the precise features of a sequence or artificial grammar before comparing studies. Early sequence learning experiments have for example compared findings even though they are based on different sequences, ranging from fixed structures (Cohen et al., 1990; Nissen & Bullemer, 1987) to ones where an artificial grammar is used (Cleeremans & McClelland, 1991; Soetens, Melis, & Notebaert, 2004). It is possible that the specific structure of these sequences can inadvertently encourage or suppress strategies that result in certain limitations to the studies. It is important to be more critical methodologically in order to identify whether learning in these paradigms, are as comparable as the literature seems to present them to be.

### **7.2.1 Differences in sequence learning paradigms**

The indications that have emerged strongly suggest that researchers should approach sequence learning experiments with some degree of caution when intending to apply findings from previous studies to their own experiments when they are not using a very similar methodology. Although this impression is maintained for specific details regarding methodological aspects, it is certainly not the case that this thesis intends to distance itself and other sequence learning experiments from each other. The thesis only suggests that details which may be considered to be minor or are even overlooked in modern research deserve more consideration. Indeed in some cases, these are features that have been addressed in the past but apparently overlooked more recently (e.g. repetitions). An example for the homogeneity of sequence learning experiments can be identified by imaging studies that have consistently demonstrated similar patterns of activity in intentional as well as

incidental designs respectively. These studies demonstrate that processing of sequential information can require the same transitions of activity, as a task becomes learnt and eventually moves to an automatic level of performance. However, it is possible that specific features of the sequence (e.g. the sequence structure, sequence length, the stimuli used) can influence the activity recorded. Consequently, areas such as the basal ganglia (particularly the striatum), frontal lobe and in some cases cerebellum can be engaged in these paradigms. Undoubtedly, imaging is a vital area of research and as technology becomes more advanced and our understanding of detailed aspects of sequence learning becomes more sophisticated, there will be ever more questions to be resolved in the scanner. Better understanding of behavioural components to sequence learning may be useful to identify why activity may be subtly different in these studies.

### **7.3. Benefits of behavioural approaches**

From the literature, it would seem that research regarding sequence learning is entering into a period of very specific questions that are probing for small details regarding what is being learnt. For this reason, behavioural aspects of cognition are becoming more relevant. Of particular interest to researchers has been the concept of consciousness (Cleeremans & McClelland, 1991; Jacoby et al., 1993; Jacoby, 1991; Wilkinson & Shanks, 2004). Debate regarding whether learning can occur in the absence of awareness has raged on for many years without any sign for there being an obvious solution. It would seem that many are now resigning themselves to the possibility that this question may never be resolved. Although the topic of awareness is an interesting one, it does seem to have occupied an excessive amount of the literature for behavioural experiments and perhaps diverted research from other fundamental issues. In this time, neuropsychological research studies appear to be growing in significance as they are providing more substantial and convincing answers based on imaging and other techniques. However, chapters 3 and 4 of this thesis have demonstrated that there are many behavioural features of sequence learning that are untapped and need to be resolved before further neuroimaging experiments are conducted. As mentioned, some of these aspects are concepts that should be revisited as research has entered into a new era where a different perspective can be borne out of early concepts.

The thesis introduces the potential for overlaps with interdisciplinary perspectives drawing from neuroscience as well as revealing the potential for working memory systems in learning of complex sequences. Performances in many of the experiments conducted are potentially dependent on the strategies and interpretations of the participants' involved. In particular, the spatial learning experiments (see chapter 4, experiment 2) have demonstrated that the



presentation of information can be an important factor behind the degree of learning that takes place. In all three experiments and the mixed and blocked conditions, the degree of information available to participants was the same, yet the learning that emerged was notably different. To some extent, this may be due to strategies that were being deployed by participants, made more feasible by spatial separations.

#### **7.4. Stimulus based learning**

Many previous studies have focused on motor and perceptual components of learning, this thesis has emphasised the significance of spatial features as an independent and significant aspect of these components. The following sections will attempt to reinterpret some information from a spatial perspective as well as offer new interpretations of data.

##### **7.4.1 Dual system learning implications from the current thesis**

There are several interesting applications that the experiments presented in this thesis have for multi and unidimensional systems for learning (see chapter 1, section 1.3.1. for detailed review). Very briefly, unidimensional learning is a purely implicit system that can only process single streams of information in parallel. In contrast the multidimensional system can process multiple dimensions of information and although it can remain incidental, awareness can be eventually achieved. First, it appears as though the experiments presented in chapter 4 would be classed as multidimensional paradigms given that learning is based on two correlated streams of information (experiments 1 perceptual -spatial, experiment 2 spatial-spatial and experiment 3 perceptual-perceptual). Given that this is the only chapter where any indications of awareness were found, the multidimensional model may provide answers for why this has occurred. The complex information provided from each of the three added dimensions may, as mentioned, be lead to greater levels of attention being paid to the sequence as well as the secondary features. Under a multidimensional system, incidental learning is potentially followed by awareness as is the case in this chapter. However, the possibility that this awareness results in better sequence learning (Curran & Keele, 1993) is not supported in this chapter. This is not to say that awareness does not improve incidental learning in sequence learning as a general principle, but that it has not occurred in this experimental paradigm. However, it is possible that learning in these paradigms is greater than the results appear to indicate. For example, some authors proposing an automatic system of learning claim that learning can be obscured under dual task (tone counting) conditions (Frensch et al., 1994, 1998, 1999). It is possible that complex task demands have attenuated learning in the colour-spatial and perceptual-colour experiments.

What remains unclear is how multi and unidimensional models of learning fit with incompatibility. Presumably, incompatibility acts as a multidimensional model where participants are learning a sequence as well as a correlated motor association. If this is the case, one may expect awareness to have taken place however, as explained in chapter 3, it was not possible to measure when using a finite grammar. Nevertheless, Koch (2007) has tested incompatibility effects using a deterministic SOC sequence and discovered that awareness is possible in these designs. However, whether this is also the case when using a probabilistic designs is not clear (Abrahamse et al., 2010), especially as Koch (2007) attributes learning to the formation of chunks of motor responses that are not sufficient as a basis for performance in probabilistic tasks.

Similarly, the remaining chapters concentrating on neurologically impaired populations seem to be as likely to result in multi as they are unidimensional systems. In these studies, participants perform a simple SRT experiment without a secondary task. Based on Curran and Keele's (1993) study, one can again assume that learning in this case is multidimensional, yet awareness is not present in chapter 5 for PDs. As mentioned, the multidimensional system is thought to involve learning that occurs in the absence of awareness. However, this learning can eventually become explicit. Nevertheless, it is not clear, when a participant becomes aware and how this transition happens. Furthermore, it should be noted that Keele and colleagues (2003) suggest that the multidimensional system relies on the ventral stream (visual processing system that can involve incidental as well as explicit information), whereas the unidimensional system is related to the dorsal stream (an implicit visual system).

As mentioned in chapter 5, there is a debate as to whether sequence learning in the PD is reliant on the ventral or dorsal striatum which are notably different processes than those described in the ventral and dorsal stream. One particular group (Macdonald & Monchi, 2011) strongly suggests that it is the ventral striatum that is responsible for sequence learning and subsequently the reason for why PDs are impaired on these tasks due to being the main area of neurological impairment from dopamine depletion. However, the dorsal and ventral streams are both thought to have some inputs to the striatum (Lawrence et al., 1998), although it is unclear whether this relates to Macdonald and Monchi's (2011) theory of ventral striatum learning and the one postulated in this thesis that it is more likely to be dorsal

#### **7.4.2 Interpretations based on the S-R rule hypothesis**

A remaining possibility is that learning may have occurred even in very complicated behavioural experiments (such as Experiments 2 and 3 in chapter 4) due to maintenance of S-R rules. Regarding the experiments discussed in chapter 4, the spatial investigations that manipulated vertical cues, have potential consequences for the S-R rule hypothesis. This is not to say that it violates S-R mapping but that it presents a complication to processing as participants cannot simply associate a response against four horizontal options but must consider a further 12 locations out of a possible 16 defined by both horizontal and vertical dimensions. As statistical analysis of the No-Cue condition (stimuli within a block appear on the same horizontal plane) revealed that learning was significantly lower than in the Blocked condition, there is reason to believe that participants are using all presented vertical and horizontal locations to learn. S-R associations in this case may not have been as simple as mapping the left most vertical boxes onto an index finger response (for right handed participants) but may have required a more complex mapping. As each response finger could be engaged by four locations, participants will have had to scan the array for longer in order to identify where the stimuli is amongst a far larger set of information than used in other SRT paradigms before making a response. Furthermore, participants were also required to incidentally learn the sequence. In the No-Cue condition, learning is based on S-R associations and may have been expected to be greater as it does not require participants to learn the changing vertical locations within each block. This may have been perceived as a less complicated S-R mapping constraint. However, the changes in vertical location per block may have been sufficient to disrupt learning enough by changing the S-R representations that were built in each block, i.e. learning maybe tied to a 2 dimensional representation of space even when changes only occur in one dimension. In this case, participants had to adapt from changing from responses to stimuli in one row to another. Therefore, although the stimuli remained the same and the mapping was the same, the S-R rule may have been slightly disturbed. Participants in the other blocks did not have the same problem as the changes in vertical locations were present throughout and so no firm reliance was associated to any one row. Instead participants were required to use a complex system of information to learn the secondary properties. Enhanced learning in the Blocked condition may have been due to a successful merger of spatial and S-R components where the blocked stimuli facilitated the ability to chunk information based on consistencies in the vertical transitions. This was not present in the Mixed condition where vertical locations were constantly changing and participants may have deemed it to be random/meaningless, or the sheer number of changes overwhelmed the available resources.

Learning in experiment 1 of chapter 4 did not benefit from this as no spatial cues were provided; instead participants' had to use perceptual features to learn. In this case, S-R associations were a lot simpler but the priming of colour cues were not strong enough for participants to use the extra information. Instead the colour seems to have created a distraction and limited the degree of learning that took place. Due to this learning of the standard monochrome condition was superior. Experiment 3 on the other hand used a more complicated perceptual design where the S-R mapping is dependent on learned associations between blocks. Again participants have to learn these associations but under a more difficult parameter than multiple vertical locations (as was the case with experiment 2).

The results of these experiments seem to indicate that learning of complex secondary constraints based on SOC sequences is achievable when information is presented in a way that does not significantly disrupt S-R associations whilst presenting spatially chunked information. It is important to note that this concept of spatial information must not be considered to be part of perceptual learning. As mentioned before, spatial information has not been clearly defined as many experiments fail to separate it from perceptual learning (Koch & Hoffmann, 2000a; Mayr, 1996). Due to this, some experiments fail to distinguish between spatial and perceptual learning. For this reason, spatial concepts should be designated as its own unique methodological constraint, separate to that of perceptual and motor components. Many studies have attempted to identify a universal rule to sequence learning, but the most logical explanation seems to be that learning is dependent on many potentially complementary components (Mayr, 1996), as has been mentioned with blocked, spatial learning (Chapter 1, experiment 2) but which can result in learning independently based on motor (Bischoff-Grethe et al., 2004; Koch & Hoffmann, 2000b; Willingham et al., 2000), perceptual (Howard et al., 1992) and spatial (Mayr, 1996) features. The defining characteristic of this learning is dependent on the specific methodology that is employed, meaning that sequence learning experiments must be approached with caution and greater consideration for their design. To this extent the task set approach to sequence learning seems to be the most reasonable as well as the most conservative. A recent review article by Schwarb and Schumacher (2012) has gone as far as claiming that implicit sequence learning experiments using the SRT should only be compared to other implicit learning paradigms (such as probabilistic classification learning such as the weather prediction task) with caution for this very reason. However, the message of this thesis would go a step further to argue that incidental sequence learning experiments in general, including SRT paradigms should not be automatically considered to be reflective of the same phenomenon. As has been seen in the chapters 3 and 4, SRT experiments can be varied in multiple ways which have implications

that we are only just beginning to appreciate. Studies have demonstrated that changing RSI's (Destrebecqz & Cleeremans, 2001), tones (Cohen et al., 1990; Frensch et al., 1998; Nissen & Bullemer, 1987), distractors (Rowland & Shanks, 2006a), mappings (Deroost & Soetens, 2006b; Willingham et al., 2000) and sequences (Kemény & Lukács, 2011) can result in conflicting results. The experiments in chapter 3 are an example of how traditional approaches such as random block analysis vs. continuous measures of learning as well as the use of repetitions can have confounding impacts on the results gathered. This is not to say that a large scale rethinking of our approach to sequence learning is required but that extra consideration for our interpretations and comparisons of results is advisable.

### **7.4.3. The role of motion cues and saccadic eye movements**

As mentioned in Chapter 4, Mayr (1996) supported the stimulus based hypothesis of learning in an experiment revealing spatial learning of objects appearing in four corners of a screen. Nevertheless, an alternate explanation for this finding and that of Howard and colleagues (1992) observational learning paradigm (See chapter 1, section 1.2.3) is presented by Willingham and colleagues (1989) who proposed that sequence learning of perceptual information is dependent on eye movements. They claimed that when eye movements are small or confined, sequence learning was impaired. This is demonstrated in an experiment where participants are trained to make responses to colour cues that appeared in one of four horizontal locations (separated by  $4.7^\circ$  of the visual field). Learning was observed when participants performed responses to sequenced colour presentations (while spatial locations were randomized) but not when locations were sequenced and colour was not. The authors argue that these saccades are a contributing factor to learning of sequential information. It is therefore possible that spatial features of Mayr's (1996) study were contributing to learning based on the significant changes in gaze direction driven by the changing stimuli. Indeed a replication of their study failed to discover perceptual learning when the visual stimuli were brought closer together (Rüsseler et al., 2003). However, Song and colleagues (2008) have challenged this assumption using a probabilistic version of the SRT where they test Willingham and colleagues (1989; 1999) hypothesis. In this experiment, the authors manipulate the distance between four targets to bring them closer to the centre of fixation, and so not requiring eye-movements. They discovered that learning of the sequence was not only possible in a group of participants who performed a traditional response based learning but also in those who only observed the task for the first stage of training before making responses at transfer. Nevertheless, this is an interesting perspective for consideration as to date little attention has been given to the effect of saccadic eye movements in sequence learning and their impact. Given the rapidly changing visual stimuli it is not clear whether

participants can detect a pattern based on eye movements that are at least strong enough to detect experimentally. However, it is clear that these eye movements are not a vital feature of sequence learning as can be seen in experiments where learning takes place based on different objects appearing in one location (Koch & Hoffmann, 2000a, 2000b; Willingham & Goedert-Eschmann, 1999) as well as studies investigating auditory (Dennis et al., 2006) or tactile (Abrahamse et al., 2010) based sequence learning. Nevertheless, it is possible that in observational paradigms, participants' are using saccades or motor planning when watching a sequence unfold. Similarly there may be learning of motion features of the stimuli (Koch & Hoffmann, 2000a, 2000b) where participants are detecting apparent movements in the sequence. This may be particularly relevant for the spatial experiment (see chapter 4, experiment 2), where targets appearing in one of 16 locations may have been formed a representation based on movements in 2-dimensional space. Further detailed investigations of this aspect of learning are required to identify the legitimacy of these claims.

### **7.5. Neurological perspectives**

An advantage to forming more concrete understandings of the mechanisms underlying learning and the information that forms its basis is that we can more accurately understand impairments in clinical populations. In chapter 1, a brief account of the imaging and patient literature was provided (see sections 1.4 and 1.5 respectively). Based on those results and as mentioned in this chapter, one can note that there are slight inconsistencies in brain activations that are reported in sequence learning experiments. Again as these studies have used different sequence structures and different stimuli displays, it is perhaps understandable that there remains conflicting accounts on their neural basis. What is certain is that the striatum is heavily involved in sequence learning and that different areas can also interact with it during sequence performance (such as the DLPFC) or even act independently to instantiate learning (such as the cerebellum).

Chapters 5 and 6 investigated the nature of sequence learning in patients who have damage to the striatum as well as fronto-striatal dysfunction. A few previous studies have demonstrated that patients with Parkinson's disease are impaired on the SRT task (Brown et al., 2003; Wilkinson & Jahanshahi, 2007), but the precise mechanism for this dysfunction was unclear. As many studies have demonstrated that l-Dopa medication can be detrimental to cognition (Cools et al., 2001; Goldman-Rakic, 1999; Williams & Goldman-Rakic, 1995) but dopamine is vital to sequence learning (Badgaiyan et al., 2007; Tremblay et al., 2009), then the effect of dopamine medication on the SRT was an important question to consider. Previous studies, using intentional designs, had addressed the issue using levodopa

transfusion (Carbon et al., 2003; Feigin et al., 2003; Ghilardi et al., 2007; Hosp et al., 2011) or raclopride (Tremblay et al., 2009). The disadvantage to these studies is that they take participants who are familiar with a certain method of taking medication and induce dopamine through invasive measures (such as PD patients given levodopa transfusions) or subject participants to totally unfamiliar conscious states (through raclopride). It is likely that under these circumstances, participants' performance will be influenced by the procedures that they go through before they even begin. However, in the present study (chapter 5), participants are tested using their normal medicated state in comparison with when they are not taking l-Dopa. This should have minimised the potential for confounding factors impacting on their performance. The results of this study support the growing evidence to suggest that dopamine plays a vital role in the incidental learning of sequenced information. It also brings to attention, the possibility that previous studies have not been engaging the appropriate cognitive systems required to facilitate processes that are benefited by l-Dopa medication. To speculate, the combination of motor features and automatic resources of learning may have been specifically pitched to facilitate better learning when l-Dopa medication was providing the extra levels of dopamine required. Based on the behavioural data discussed of in previous chapters and the discussions provided in chapters 3 and 4, it is interesting to consider whether extra resources from attention or even incompatibility would remove or even reverse this effect in PD. As it is accepted that l-Dopa impairs most cognitive functions and it is unclear whether the use of distractors or multiple/concurrent learning is harnessing additional resources such as working memory properties, it may be expected that participants performing a spatial (see experiment 2 of chapter 4) or perceptual (see experiment 3 of chapter 4) SRT tasks may perform better when they are not taking medication.

It is an obvious possibility that impairment, or attenuation, of learning in patient groups can be down to motor problems. This is particularly relevant in a disorder such as PD. However, as the literature strongly suggests that the striatum is involved in incidental learning, and participants with PD have been demonstrated to be impaired in non-motor specific procedural tasks (Knowlton et al., 1996), it is understandable that learning in the SRT may be affected due to cognitive difficulties. Chapter 6 advanced the investigation into neurological illnesses by assessing the impact of stimulation to the GPi in dystonia. As previous papers have implicated the involvement of the GPi in sequence learning (Brown et al., 2003; Carbon et al., 2004; Ghilardi et al., 2003), this was an important issue to address. Results indicated there were no noticeable differences between participants with dystonia and healthy age matched controls, indicating that structural damage in dystonia does not alter

incidental sequence learning. Furthermore, there were no differences between patients who had received DBS of the GPi or not. At first glance, these findings suggest that DBS of the GPi in dystonia does not modulate incidental learning on the SRT. However, as discussed in chapter 6, there are emerging theories in the dystonia research that point to plasticity in the brain rewiring dysfunctional fronto-striato circuitry to instead engage the cerebellum. This is a largely untapped area of research in incidental sequence learning, particularly with the SRT task. As mentioned in the chapter 6, there is evidence to suggest that the cerebellum is active in sequence learning particularly in intentional designs (Carbon et al., 2003; Ghilardi et al., 2007). Furthermore the cerebellum has been activated in some incidental tasks (Doyon et al., 1996). However, research in dystonia, demonstrating this activity has been demonstrated with intentional designs that are engaging slightly different strategies. Although there is some evidence to demonstrate that the cerebellum can be active in incidental sequence learning, more attention is needed to isolate this potential. Again a combination of behavioural and neurological data is the key to understanding this process. Furthermore computational models have done much to reveal the interaction between the frontal lobe and the striatum or cerebellum. It is possible that, although the cerebellum is not the primary centre for activity in sequence learning, it is nevertheless a useful area to achieve learning. If it is true that patients with dystonia have structural problems in the striatum, they may be ideal candidates to image whilst performing an incidental SRT. This would greatly help to resolve some of the unanswered questions raised by the results in chapter 6. If it is demonstrated that these participants are activating the cerebellum, it would suggest that stimulation of the GPi is irrelevant in this population. Subsequently, the GPi may yet engage in sequence learning in an incidental SRT task but as patients with dystonia have already redirected activity to the cerebellum, it is not as active as in healthy populations. However, if they are in fact activation the striatum as would be expected in healthy participants, the study will have demonstrated that the GPi does not influence learning on this task. Until this question of neural activity in this specific paradigm has been resolved, it is difficult to establish which is more likely.

### **7.5.1 Neuroimaging and the SRT**

Based on behavioural evidence, there is still much that is unclear regarding sequence learning and in particular the SRT. As this is becoming a commonly used design to use with SOC sequences, it is important to gain a better understanding of the neurological principles involved. The thesis has dedicated a significant proportion of time discussing the need to re-establish our understanding of methodological principles. One way of developing our understanding is to investigate the impact of methodological alterations on brain activity. As



it is the assertion of this thesis that subtle changes to task design can influence strategies and performance, it is possible that such activity may reveal different mechanisms. In particular, deterministic designs seem to implicate a different range of performance components than probabilistic presentations. For example, one might speculate that participants' performing deterministic sequences may develop an automatic level of performance at a far earlier stage than probabilistic learners. Considering that the sequence in the former does not deviate from the fixed structure, motor associations may be easier to form due to the fixed response sequence. In contrast, probabilistic sequences deviate from the fixed structure meaning that participants' must cope with the eventuality that the sequence will change. It is difficult to predict the effect that this may have on the way participants perform and the impact that it may have on neural activity. However, there is a clear difference in the strategies that are and are not possible for both. Whether this is sufficient to engage different neural activity is yet to be established. Should this be confirmed, it would directly implicate the changes in methodology with alterations to behavioural and neural mechanisms.

As mentioned, imaging of patients with dystonia may provide further clarification regarding neurological as well as behavioural components to sequence learning using the SRT. As the cerebellum has been activated in these participants in incidental sequence learning designs, although they are often found to be impaired on these paradigms (Carbon et al., 2004, 2011; Ghilardi et al., 2003), it is not clear whether the same area would be involved in incidental versions of the SRT. Furthermore, the probabilistic feature of the SRT may present further implications that could modulate activity. If participants in dystonia are not using the striatum to learn, it would provide important consideration for our understanding of the field.

The many behavioural experiments that have been conducted prior to these neuro-scientific studies have laid the foundation for these advancements. However, there remains a need to better understand these very complex neurological interactions. The results in this thesis have demonstrated that there are many basic concepts that have been taken for granted in the literature and which can have consequences on our understanding and interpretation of imaging data and results from patient populations. It is vital that research first clarifies the potential influence of these before addressing more advanced questions in neuroscience.

## **7.6. Discussion of limitations**

All of the experiments performed in this thesis have involved variations of the traditional SRT paradigm. It was important to maintain a common frame of reference across these chapters as the investigations conducted aimed to develop our understanding of sequence learning using novel approaches. Having maintained the same sequential structure for most

of the experiments facilitates the comparison of results across studies compared to other cases where authors attempt to compare results across studies using different methodologies. That said there are several alternative considerations that were not explored and which may have improved the quality of the findings. These will be discussed here.

Chapter 3, experiment 1, employed an orthodox SRT paradigm with the additional constraint of incompatibility for one conditions. Considering that one of the major findings in this chapter was the effect of learning metrics, it may have been useful to identify the consequence of using a random block in the first experiment where learning was only measured probabilistically. This was not originally included as the influence of learning metrics were not fully appreciated at that point. Subsequent studies may choose to explore this potential; however, there is reason to believe that the effect of a random block in this case will not be as dramatic as in experiment 2, as trials are presented probabilistically with SOC properties which may disrupt the degree of priming required to build a reliance on the set sequence. Furthermore, the absence of repeat items may diminish this effect even further.

Chapter 4 explored the potential for enhancing learning using additional cues. One possibility for why learning had not been greater in the two colour cued conditions for experiment 1 is that they were not salient enough. An alternative approach would be to make the stimuli appear as coloured squares where the surface area of the stimuli is greater than that of an 'x'. Perhaps this would have helped to emphasise the colour more. A further limitation is that participants were not screened for colour blindness using any formal tests. However, as the vast majority of participants were women, and the incidence of colour blindness in women is very low, this was deemed to be unlikely to have had a large influence on the results. More importantly, there could have been an extended training period for experiment 3 as participants were learning a more complicated mapping between stimuli and motor responses. In this case, it is possible that participants would have obtained a greater learning score with extended training, which would have facilitated identifying enhanced learning in dual cue conditions. Nevertheless participants were able to obtain a significant level of learning in most of these conditions with an equivalent length of training to experiments 1 and 2.

Chapter 5 introduced the relevance of neurological patients to sequence learning. In doing so, the chapter demonstrate the effect of medication on learning. However, an important consideration for testing patients is to consider the variability of their condition. The thesis attempts to resolve this by screening for mood and IQ and to match all participants for stage of illness. Nevertheless, there are occasions when patients are having particularly bad days

with respects to the severity of their specific symptoms (tremors etc...). Consequently, this can have an additional effect on performance in the task. This is perhaps more likely when participants are tested after a period of withdrawal from their medication. Therefore, to some extent, the effect of learning in the off medication condition may have been partly contributable to the lower learning scores.

Chapter 6, is perhaps subject to similar confounds to chapter 4, particularly due to the variations in gene status in dystonia. As mentioned, there are several classifications of dystonia which determine whether the mutation is genetically contracted or not and what particular form it is (dwt1, dwt2 etc...). A further important criterion is the manifestation of the disease and whether it is focal (effecting one general area such as hands or neck etc...) and in particular focal hand dystonia (limited to hands) or writer's cramp (again affecting the hands). In these cases the performance of a participant may be worse than that of another individual with cervical (shoulders and neck) dystonia as they are not able to use the button box as effectively. However, it should be noted that all participants who were not able to use their fingers (and so those with severe focal hand and writer's cramp) were excluded based on their poor performance. Similarly, those with marked symptoms from other manifestations of dystonia that may have affected their performance were excluded from the study. In this sense, there is a general limitation to testing patient populations that cannot be escaped, which is that some participants' symptoms are going to interfere with their performance. Importantly, there are very few studies published in dystonia investigating their performance on incidental sequence learning. As this is the first to do so using the probabilistic SRT, the findings are of relevance to our understanding of the disease, particularly, as most previous studies have used a similarly heterogeneous sample. Further, investigations using the same task can benefit from recruiting a more selective sample.

On a more general level, the issue of variability across all experimental chapters is valid in that participants are likely to produce inconsistent RTs (Hultsch, MacDonald, & Dixon, 2002). As mentioned, this is an interesting element in PD as patients already have variable neurological symptoms that may be contributing to their performance. Furthermore, intra-individual assessments propose an interesting comparison between the estimates of learning taken through a mean of RTs and whether this is consistent with the wider sample of all recorded responses. It has been argued that the mean may not capture the degree of individual inconsistency in RTs, which may be a critical component in changes in both normal and pathological performance. Furthermore, this inconsistency may be accentuated in later stages when fatigue is most relevant (Bunce, MacDonald, & Hultsch, 2004). This may be particularly interesting to look at in the SRT when learning is usually assessed in later

stages of the task. However, a benefit, as mentioned, with probabilistic learning is that a measure can be taken across blocks and at different time intervals. As demonstrated in several of the chapters, time did not seem to be particularly crucial to the estimate of learning. However, further assessment of variability across blocks may produce further interpretations.

The preferred method for measuring learning in the SRT tasks has tended to be through absolute difference scores (Sutton, 1988). When averaged across participants it has often been assumed these scores are not unduly influenced by individual variations in mean RT in sequence learning experiments. As the overwhelming majority of studies in this area have adopted this methodological approach, the experiments in this thesis chose to maintain this core measure in order to make findings comparable. Nonetheless, the possibility remains that measuring learning through this technique may produce disproportionate estimates of learning due to magnitude differences in RTs between individuals. However, this assumes that the absolute difference between probable and improbable trials is proportional to RTs (Jimenez et al., 1996). As discussed in Chapter 3, Deroost and Soetens (2006b) have discovered that there are no significant proportionate scaling issues in learning estimates when a more complex perceptual task (which evokes slower RTs) is compared with a less complex (involving faster RTs) one. Nevertheless, it is possible that more detailed accounts of variability in these studies are a potentially important aspect that has been thus far overlooked. Considering the intraindividual differences between participants (healthy as well as neurological patients), an investigation of whether these scaling issues in RTs contribute to an over or underestimation of learning is prudent. Furthermore, a full explanation for differences in RTs that occur within conditions resulting in some participants performing faster than others are not necessarily satisfied by absolute difference score calculations (Bertelson et al., 1963). Instead, a more detailed assessment of variability may be required to identify whether there are any additional behavioural implications for it.

A further consideration can be applied to the number of participants in each experimental condition. Many studies consider ten participants to be sufficient in sequence learning experiments but given the null effects of some of the findings in this thesis, it is worth briefly considering the issue of power in these task. In some cases studies have used greater numbers of participants in order to reach the findings that they publish. It is therefore, possible that experiment 3 in chapter 4 and the studies in chapter 6 may have benefitted from having more participants. However, given that there were no real trends towards significance in these studies, no further consideration was given to the likelihood that more participants may have produced an effect. Furthermore, the findings in other experiments using ten or

eleven participants that did reach significance, demonstrate the robustness of the general methodological design. Therefore, any significant deviations from this consistency in order to find an effect may be considered to be an excessive attempt to find an effect.

Finally, Bonferoni corrections were not made as it is often accepted that Bonferoni corrections provide a fairly conservative estimate of significance, potentially meaning that it may underestimate the degree of learning that is presented. As the number of post-hoc tests were generally small it was decided that the modest increase in the risk of a type 1 error was outweighed by the large increase in likelihood of a type 2 error. Furthermore, when multiple post-hoc tests are significant the p value is again at or approaching 5%.

### **7.7. Conclusion**

There appears to be sufficient evidence to suggest that our understanding of sequence learning requires a more conservative approach than that which is exercised by some researchers. The results of this thesis demonstrate that learning can be dependent on the learning metric, the sequence structure and spatial dimensions. Furthermore, the understanding of what constitutes spatial learning is a topic which requires more attention. It is proposed that spatial components cannot simply be considered as a perceptual feature as its contribution to learning is too important to be marginalised as a sub-feature of perceptual learning. Furthermore, a clear distinction between incidental and intentional as well as probabilistic and deterministic sequences is required to avoid confusion between the very different methodological and practical constraints of these paradigms.

Data from neurologically impaired participants suggest that sequence learning is different to some cognitive processes in that it involves an associative loop combining motor and visual components that can be improved by l-Dopa medication in PD. Results also suggest that more research is required into dystonia, to identify the precise areas of the brain that are being used to learn information in the incidental SRT. As evidence from intentional studies demonstrated that activity can exist in the cerebellum and computational models have predicted this areas role, there is reason to believe that dystonia patients in this study could have used the cerebellum to learn.

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