Cognitive control of sequential behavior

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COGNITIVE CONTROL OF SEQUENTIAL BEHAVIOR

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1 General introduction

We interact with the world through movement. When we talk, dance or type we perform movements in order to interact with the world around us. Most actions we perform in everyday life consist of series of simple movements. For example, we lace our shoes in one fluent movement while it actually consists of a series of several more simple movements. Without practice it takes hard work and a lot of attention to lace a shoe, but with practice this can be done, and usually is done, without attention. This skill of lacing shoes illustrates that we can sequence simple movements in a specific order to attain fluent execution of more complex movement patterns. The execution of these motoric sequences is initially slow, variable and needs a lot of attention, but with practice execution becomes fast, stable, and automatic, which results in skilled human motor performance. This ability to sequence movements is one of the hallmarks of human cognition, as, for example, it enables us to speak, to play a musical instrument and perform sports (Keele, Ivry, Mayr, Hazeltine, & Heuer, 2003). This thesis deals with the mechanisms underlying motoric sequence learning as studied with a particular task: the discrete sequence production (DSP) task. Furthermore, we investigated if the mechanisms underlying motoric sequence learning also help in our understanding of problems people experience that are diagnosed as dyslectics, as dyslexia has been suggested to be related to motor sequence learning (e.g. Hari & Renvall, 2001).

1.1 Phases of motor learning

Motor learning can be defined as "a set of processes associated with practice or experience leading to relatively permanent changes in the capability for movement" (Schmidt & Lee, 2005). Three main phases can be distinguished in motor learning: a cognitive, an associative, and an autonomous phase (Fitts, 1964; Anderson, 1982). In the cognitive phase, the problem has to be solved what movement exactly has to be performed. For example, when learning to play the violin it has to be discovered how to hold the violin, how to keep the bow in your right hand, where to place the fingers on the fingerboard, etc. In this phase useful strategies are preserved, while performance can still be very inconsistent and variable. During this phase performance is largely verbal-cognitive in nature and performance gains of limited practice are high. In the associative phase, the learner has determined her most effective strategy, and more subtle adjustments can be made. For example, in this phase a violinist makes subtle adjustments in finger placements on the fingerboard. Performance becomes more consistent, gains are small and

performance is probably motoric in nature, which means that it is related to specific effectors/muscles. Finally, during the autonomous phase the skill has become automatic in the sense that it lacks interference from particular secondary tasks. In this phase, one can attend to other aspects of the task and the impression is given that the skill can be performed without attention. For example, a professional violinist can focus on emotional aspects of a piece of music, and on other musicians in the orchestra, without focusing on where to place their fingers. Thus, with practice performance gains decrease and skills become automatic.

1.2 Discrete sequence learning

To study the acquisition of complex movement patterns, the learning of discrete sequential finger movements can be used. In line with the violinist example, discrete sequence learning of movements is thought to pass through three phases (Verwey, 2001; Hikosaka et al., 1999). The first phase is the stimulus-response phase, in which stimuli are individually translated to their appropriate response. The second phase is the cognitive phase in which movement sequences are controlled at a cognitive level, for example at a spatial or abstract level. The third phase is the motoric phase in which movement sequences are controlled at a motoric level and sequence execution becomes fully automatic, which means that no attention is needed to perform the movement sequence. So, similar to motor learning in general, with practice improvements in motoric sequence behavior decrease and motoric sequence performance becomes automatic.

A task that is well-suited for investigating motoric sequence learning is the DSP task. In a typical DSP task, several discrete sequences are practiced extensively by responding to fixed series of mostly three to seven key-specific visual stimuli. All but the first stimulus are presented immediately after the response to the previous stimulus, and there typically is a limited number of sequences. During the task, usually four to eight aligned square placeholders are shown on a display. At the start of a sequence, the squares are filled with the background color (black). After a certain time interval one square is filled with a color, to which participants react by pressing the spatially corresponding key. Immediately after a key press another square is filled, and so on. If a participant presses a wrong key, an error message is given and the same square is filled again until the correct response is given. After execution of a sequence the next sequence starts, again preceded by squares being filled with black (See Figure 1.1).

Another task to study motoric sequence learning is the serial reaction time (SRT) task (Nissen & Bullemer, 1987). Stimulus presentation and response execution are largely identical to the DSP task, but in the SRT task, participants

continuously cycle through a fixed series of 8-12 keypresses, and there usually is an interval of about 200 ms between a response and the next stimulus. Learning in the SRT task is measured by contrasting the average response time of the repeating pattern with the average response time to stimuli which occur in a random order. Since participants may be unaware of the repeating movement sequence, the SRT task is suitable for studying explicit and implicit motoric sequence learning. In contrast, the DSP task is suitable for studying discrete motoric sequence learning, as is done in this thesis, implying a focus on preparation and segmentation of these sequences.
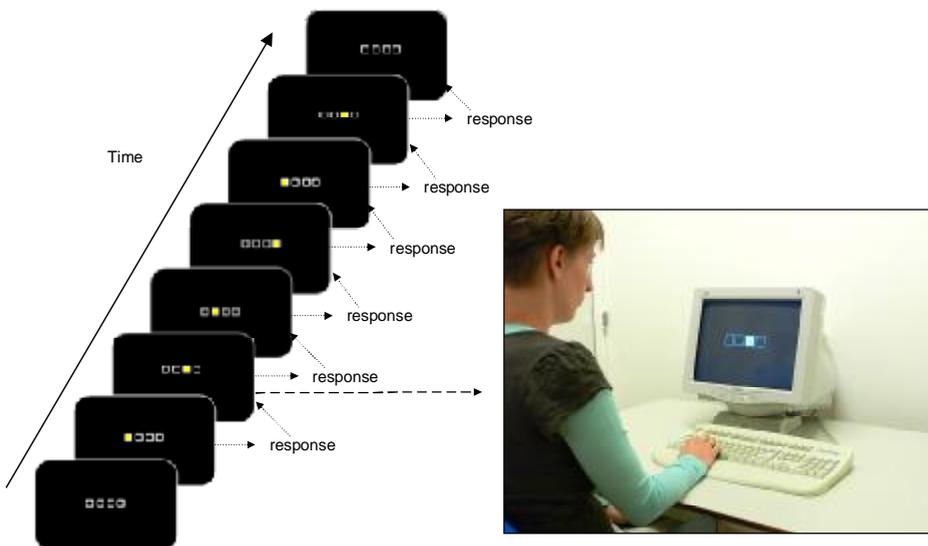
Figure 1.1 Task layout of the DSP task. Participants respond to each filled placeholder by pressing the corresponding key.

1.3 Phenomena in the DSP task

In the DSP task, discrete movement sequences of limited length are practiced thoroughly, which makes the DSP task suitable for investigating sequence segmentation, effector-dependent sequence learning, and hierarchical control (Verwey & Wright, 2004; Rhodes, Bullock, Verwey, Averbeck, & Page, 2004; Verwey & Dronkert, 1996). Some consistent effects are found with discrete

sequence learning of movements, which will be described in the following paragraphs.

Segmentation

Some keypresses within a longer sequence are executed consistently slower than other keypresses, which is assumed to index the segmentation of motor sequences (Verwey, 1996). If there are regularities in a sequence in spatial, temporal or conceptual ways, all participants are likely to use the same segmentation patterns (Koch & Hoffmann, 2000b). However, if such regularities do not occur, participants will segment the sequence anyway, but segmentation patterns may differ between participants (Verwey, 2003b; Verwey & Eikelboom, 2003; Sakai, Kitaguchi, & Hikosaka, 2003). This suggests there is some limit in segment length, for example due to a motor buffer limit.

As segments consolidate with practice, it is suggested that each segment involves the execution of a motor chunk (Verwey & Eikelboom, 2003). The notion of chunking in working memory was introduced by Miller (1956), who defined a chunk as a memory representation within which several memory items can be treated as a single processing unit. Since the mean memory capacity in working memory is thought to consist of 3-5 chunks (Cowan, 2000) chunking increases the number of items that can be kept in memory. In line with Miller (1956) and Cowan (2000), a motor chunk is thought to represent several movements represented by a single memory unit, which thereby increases the number of movements that can be kept in the motor buffer. Selection of a motor chunk may be conceived of as a result of the loading of all individual elements of that segment into the motor buffer in a single processing step, therefore, chunking speeds up the selection and initiation of familiar segments (Verwey, 1999). However, with extensive practice, indications for segmentation may (partially) disappear (Verwey, 1994), which may be caused by the faster initiation of the chunks or by the integration of chunks into longer super chunks.

It appears that there is no fixed chunk size in sequence learning. Results of a data entry task suggests that there is an optimization strategy whereby the processing costs of chunking are weighted against the processing costs of short term memory (Fendrich & Arengo, 2004). More specifically, when a sequence is segmented into a few large chunks the processing costs of chunking will be high, as chunks are large, and the processing costs of short term memory will be low, as a few items have to be kept active. In contrast, when a sequence is segmented in a large number of short chunks the processing costs of chunking will be low, as chunks are small, whereas the processing costs of short term memory will be high, as many items have to be kept active. However, the extent to which chunking

strategy is under conscious control has not yet been addressed (Fendrich & Arengo, 2004).

Sequence length effect on latency

With increasing sequence length, the response time to the first stimulus increases: the so-called sequence length effect on latency (Verwey, 1994; Sternberg, Monsell, Knoll, & Wright, 1978). This effect on the first response is thought to be due to the preparation of a whole sequence before response initiation (Kennerley, Sakai, & Rushworth, 2004), which consists of the selection and programming of individual responses or motor chunks (Verwey, 2003b). However, recent studies indicate that not the entire sequence has to be prepared before initiation, but that preparation can be distributed across periods before and during sequence execution (Van Galen & Weber, 1998; Rosenbaum, Hindorff, & Munro, 1987). Furthermore, the preparation of an individual keypress may also start while executing the previous keypress, which makes it possible to rapidly produce sequences of keypresses (Verwey, 1996, 2001). Thus, the parallel occurrence of selection and motor execution during sequence learning may result in the rapid execution of sequences in the DSP task. In line with this, Verwey (1999) found that with highly practiced sequences in the DSP task there was no sequence length effect on latency, but instead the response to the first item of a chunk was slowed. Verwey, (2003b) reasoned that only the selection of a chunk, and not the programming, can overlap with the preceding segment, as programming may involve the reloading of the motor buffer.

Sequence length effect on rate

With increasing sequence length, the mean element execution time increases, which is indicated as the sequence length effect on rate (Sternberg et al., 1978; Verwey & Eikelboom, 2003; Verwey, 2003b). The sequence length effect on rate remains with practice and does not increase with serial position within the sequence (Verwey, 2003b). This effect is caused by individually different segmentation patterns, which results in a few long interkey intervals at different positions, and thus increases average execution rate. Occasionally long interkey intervals, which cause the sequence length effect on rate, are in line with the idea of distributed programming. Furthermore, the sequence length effect can also be caused by more extensive preparation of the first few elements of a sequence, which results in a decreased interkey interval at the first positions.

Effector specificity/transfer

In motor control tasks, the dominant hand is typically found to perform better than the non-dominant hand (Annett, 1992). Though, after extensive practice in the DSP

task, practiced sequences were executed faster with practiced effectors as compared with unpracticed effectors, irrespective of hand dominance, indicating effector specific sequence learning (Verwey & Wright, 2004). In addition, after extensive practice in the DSP task, the unpracticed hand executed the practiced sequence faster than a new sequence, indicating effector-unspecific sequence learning (Verwey & Wright, 2004). It is thought that initial sequence execution relies on effector-unspecific sequence knowledge and with practice execution becomes more effector-specific (Verwey, 2001; Hikosaka et al., 1999). Thus, part of sequence learning in the DSP task is hand and sequence-specific, whereas another part of sequence learning in the DSP task is only sequence–specific.

Execution of mirrored versions of practiced sequences (from now on called mirrored sequences) with the unpracticed hand leads to the movement of the homologue fingers of the unpracticed hand. However, the execution of mirrored sequences with the practiced hand leads to the movement of different fingers of the practiced hand. Different representations are used during the execution of mirrored sequences with the practiced and the unpracticed hand; a mirrored sequence executed with the unpracticed hand can use a general motor representation of the movement in which the fingers are specified, but not the hand, whereas the mirrored sequence executed with the practiced hand can not use such a representation. In the SRT task partial transfer was observed when mirrored sequences were executed with the unpracticed hand, whereas there was almost total transfer when practiced sequences were executed with the unpracticed hand (Grafton, Hazeltine, & Ivry, 2002). In contrast, with extensive practice Verwey and Clegg (2005) showed partial transfer when the practiced sequences were executed with the unpracticed hand. However, Verwey and Clegg (2005) also showed that the execution of practiced sequence with the unpracticed hand was faster than the execution of mirrored sequences executed either with the practiced hand or with the unpracticed hand. Thus, in the SRT task there is more transfer to the unpracticed hand when the practiced sequence is executed than when the mirrored sequence is executed, suggesting that sequences are partially stored in a visual-spatial nature. It is unclear if this is also the case for the DSP task. If there is transfer to mirrored sequences in the DSP task it could be that effector unspecific sequence knowledge can be used by either hand, which still has to be mirrored, or it could be that the effector specific knowledge is translated to the other hand (Grafton, et al., 2002).

Conclusion

Longer discrete keying sequences are segmented with practice, which reflects the development of motor chunks. This segmentation results in the delayed execution of long sequences as compared with short sequences and in the delayed

execution of the first stimulus of a sequence or chunk. With extensive practice, signs of segmentation might disappear, since the preparation and execution of movements overlap. These phenomena in discrete keying sequences are in line with a distributed programming view, which suggests that preparation and execution movements occur in parallel. Finally, with practice in the DSP task effector-specific and effector-unspecific learning develop, but it remains unclear what knowledge transfers to mirrored sequences.

1.4 Representations

If we learn movement sequences, how is the sequence represented in human memory? Since motor sequence learning develops through different phases it has been suggested that different representations are involved that code relevant information. For example, skilled movement sequences have been argued to involve spatial and nonspatial representations (Bapi, Doya, & Harner, 2000; Koch & Hoffmann, 2000a; Mayr, 1996), as well as effector-dependent and effector-independent representations (Hikosaka et al., 1999; Verwey, 2003a, Miyapuram, Bapi, & Doya, 2006). The different representations are probably hierarchically organized, which means that some representations are more abstract, such as the spatial and the nonspatial representations, and other representations are more concrete. Also, different representations are likely to develop at different rates with practice (Keele, Cohen, & Ivry, 1990). For example, Shin and Ivry (2002) had participants perform an SRT task in which the spatial sequence (indicated by the stimuli) and the temporal sequence (indicated by the stimulus-response interval) were varied. This resulted in a temporal and a spatial sequence, which could correlate or not. They showed that the visual-spatial sequence was learned irrespective of a correlating temporal sequence, whereas the temporal sequence was only learned when it correlated with the spatial sequence. This suggests that first the visual-spatial sequence is learned and subsequently the temporal sequence is learned. A way to investigate representations is to study transfer from a learned condition to another condition. For example, the amount and pattern of transfer from sequence execution with a practiced hand to an unpracticed hand can give us information about the effector-specificity of representations.

Implicit/explicit learning
Representations can involve implicit and explicit knowledge. One view on implicit and explicit representations is that they are two endpoints along a continuum (Cleeremans & Jiménez, 2002). The availability of information to consciousness is thought to depend on the quality of the representation, which increases as it gains strength, stability over time and distinctiveness (Cleeremans & Sarrazin, 2007).

Thus, when the quality of a representation increases, sequence knowledge can be accessed by multiple systems and, therefore, may become explicit. This suggests that consciousness is a process rather than a property of a state (Cleeremans & Sarrazin, 2007). For the DSP task this suggests that with practice, as representations become more stable, sequence knowledge will become more explicit. Another view on implicit and explicit representations is that they are acquired in parallel and that implicit knowledge may affect performance, even if it hinders the expression of explicit knowledge (Curran & Keele, 1993; Keele et al., 2003). For the DSP task this suggests that both implicit and explicit knowledge may exert their influence over practice.

Frames of reference

Research on motor learning has also been concerned with the frames of reference in which movements are planned and controlled, which are the spatial codings of objects relative to a reference point (Witt, Ashe, & Willingham, 2008). Movements can be planned with respect to intrinsic, spatial (body-based) coordinates (Hammerton & Tickner, 1964; Rosenbaum & Chaiken, 2001; Lui, Lungu, Waechter, Willingham, & Ashe, 2007; Grafton et al., 2002) and/or with respect to extrinsic, spatial (world-based) coordinates (Rosenbaum & Chaiken, 2001; Lui et al., 2007; Grafton et al., 2002). As a consequence, reference frames can be egocentric, which uses some part of the body as a reference point, and/or allocentric, which uses a reference point external to the body (Witt et al., 2008). Multiple egocentric reference frames are possible such as a head-, hand- or body-centered reference frame, and multiple allocentric reference frames are possible such as room- or response board-centered reference frame (Witt et al., 2008; Heuer, 2006; Colby & Goldberg, 1999). These egocentric and allocentric reference frames can be simultaneously active. Single cell recordings in monkeys are the primary evidence for multiple forms of spatial frames of reference (e.g. Snyder, Grieve, Brotchie, & Andersen, 1998; Andersen, Snyder, Bradley, & Xing, 1997; Rizzolatti, Fogassi, & Gallese, 1997). During these recordings, the receptive field of a group of neurons, which is the spatial location in which a stimulus makes a group of neurons fire, was studied. If this receptive field changes when a body part is moved then those neurons code space relative to this body part.

Several authors have proposed that motor behaviour is supported by egocentric representations (Jeannerod, 1994; Rossetti, 1998). In addition, Willingham (1998) suggested that perceptual-motor integration and sequencing processes rely on an egocentric representation. This suggests that the representation underlying sequence learning with the DSP task is most likely egocentric. In line with this, Witt, Ashe, and Willingham (2008) showed that, using the SRT task, sequences were coded in an egocentric reference frame, which was

not hand-centered but possibly eye-, head-, or torso centered. Eye-, head-, or torso centered reference frames make it possible to execute the sequence with either hand, which is in line with the transfer from practiced sequences to mirrored sequences, as discussed before. More specifically, it was suggested that with practice, sequence learning in the SRT task can become more effector-specific, which can coincide with a shift from a head- or torso-based reference frame to a hand-centered reference frame (Witt et al.,2008; Verwey, Abrahamse, & Jiménez, in press). However, Lui et al. (2007) showed that during explicit sequence learning transfer occurred when the egocentric or the allocentric reference frame was changed, however, no transfer occurred when both reference frames were changed. This indicates that explicit sequence learning comprises both egocentric and allocentric reference frames. In line with these findings, it is suggested that initial sequence learning in the DSP task can rely on egocentric and/or allocentric reference frames, and that with practice, the hand-centered reference frame will become more important.

Conclusion

Different, hierarchically organized representations develop at different rates with practice in the DSP task. People are able to switch between the representations they use (Verwey, 2003a), which are likely to have different reference frames. Furthermore, it has been suggested that different representations develop in parallel, with processors operating on these representations that race against each other to trigger the next sequence element (Verwey, 2003a). However, it has also been proposed that representations develop on top of each other. For example, an effector-dependent representation may come on top of the effector-independent representation, with the effector-dependent representation being adjusted to the mechanical properties of the used effectors (Verwey & Wright, 2004; Verwey & Clegg, 2005). Finally, with practice in the DSP task knowledge becomes either more explicit due to transfer from stable representations, or implicit and explicit knowledge may coexist in parallel.

1.5 Models

Several models have been proposed to describe the learning of discrete movement sequences. Verwey (2001) proposed that a cognitive and a motor processor underlie the production of discrete motor sequences. The cognitive processor is thought to initially select a representation of a sequence, based on a symbolic representation, and subsequently this representation is read and executed by the motor processor. The cognitive processor is additionally involved in planning and organizing the goal structure of movements (Shaffer, 1991). Initial execution of a

sequence will induce a high demand on the cognitive processor, as each element in the sequence has to be selected separately, whereas with practice, the demand on the cognitive processor will decrease, as integrated and complex parts of a sequence (i.e. motor chunks) can be selected at once. Subsequently, the motor chunk, or separate elements in case of initial learning, can be loaded into the motor buffer by the cognitive processor, after which the sequence is executed by the motor processor. It is unclear if the execution of the sequence by the motor processor is dependent on learning; for example, it could be that the execution of a chunk is less demanding than the execution of individual responses. Finally, this model suggests that initially the cognitive processor acts upon abstract representations, using it to create a temporary motor representation in the motor buffer, and with practice the motor processor relies upon motor representations that are directly available (Verwey, 1996).

A second model describing discrete sequence learning is the model of Hikosaka et al. (1999). Hikosaka et al. (1999) based their model on a trial-and-error button press task in which two out of 16 buttons are simultaneously illuminated. The participant (often a monkey) has to press the two buttons (a set) in the correct predetermined order, which is found out by trial and error. After the correct completion of a set a second set is presented, and is to be pressed again in the right order, and so on until the fifth set (a hyperset). When a wrong button is pressed the participants starts again with the first set of the hyperset. A hyperset is presented for 10-20 successful repetitions and subsequently a new hyperset is presented. The model of Hikosaka et al. (1999) proposes that when a sequence is encountered for the first time (pre-learning phase) every single stimulus is translated into a single response, which probably relies on stimulus or response-based representations. In addition, with practice, sequences become represented in parallel at a spatial and at a motor level. The processor at the spatial level, which relies on spatial representation and which is effector-unspecific, is thought to be most active during the initial phases of learning, whereas the processor at the motor level, which relies on motor representations and which is effector-specific, is most pronounced during later phases of learning. Sequences are learned by both processors simultaneously, but either processor may have a more important contribution, depending on the behavioral context and the level of practice.

The spatial processor of this model is somewhat similar to the cognitive processor of the model of Verwey (2001), as it is effector-unspecific and most active during initial learning. Furthermore, both processors rely on an abstract representation, which could be spatial. However, the spatial processor of the model of Hikosaka et al. (1999) directs the movements themselves; whereas the cognitive processor of the model of Verwey (2001) directs the motor processor and not the movements themselves. Consequently, the model of Verwey (2001) predicts that

with practice the demand on the cognitive processor decreases and the demand on the motor processor remains the same, whereas the model of Hikosaka et al. (1999) predicts a decreased demand on the cognitive/spatial processor and an increased demand on the motor processor. Thus, the spatial processor of the model of Hikosaka et al. (1999) and the cognitive processor of the model of Verwey (2001) are not identical.

A third model describing sequence learning is the dual-substrate model of sequential representation by Keele et al. (2003). This model is based on the SRT task and describes sequence learning in a broader context of human cognition, but seems also applicable to the DSP task as it corresponds with the parallel development of several representations in the model of Verwey (2001) and Hikosaka et al. (1999). The model proposes two types of systems working in parallel: a set of unidimensional systems and a multidimensional system. Unidimensional systems automatically extract regularities from a single dimension (without attention) and form associations between responses within that dimension. Since the unidimensional system has no access to other higher-level system, due to its encapsulated nature, regularities remain implicit. As a result the unidimensional systems use un-interpreted stimuli and are not subject to disruptive information in other dimensions. In contrast, the multidimensional system builds associations between events (which can be of different dimensions) if one event predicts an ensuing event. The multidimensional system uses categorized stimuli as it only selects stimuli relevant for the task at hand. This multidimensional system is subject to dual-task interference, which is caused by a lack of correlation between the attended information (and not by informational overload). Thus, unidimensional systems extract regularities within one dimension, whereas the multidimensional system can additionally extract regularities between dimensions when multiple dimensions are attended. Moreover, before the specification of effectors the representation used by both systems is relatively abstract (Keele et al., 2003). Finally, the unidimensional systems rely on concrete representations, like stimulus-based or response-based representations, whereas the multidimensional system relies on more abstract representations, like spatial representations.

Largely similar to the dual-substrate theory of Keele et al. (2003) is a different model of Verwey (2003a), which constitutes of a general purpose processor (multidimensional system) and several single purpose processors (unidimensional systems). All these processors can work in parallel, without being integrated, and race against each other, to trigger the next response. The general purpose processor, which is at an abstract - maybe verbal - level, uses a set of rules to trigger the next response (for example a stimulus-response transformation rule). In contrast, the single purpose processors simply translate input into output

patterns and learn by forming associations between input and output. The general purpose processor can work in different modes, by using different inputs. The relation between the model of Verwey (2001) which constitutes of a cognitive and a motor processor and the model of Verwey (2003b) which constitutes of single purpose processors and a general purpose processor is unclear, as they explain different types of results.

Overall, these models suggest that sequence learning in the DSP task is initially based on stimulus-response learning and with practice multiple representations develop. These representations develop in parallel and can be at a motor, spatial, or at a still different level. The effector specific representation is suggested to be at a motor level, whereas the effector unspecific representation is suggested to be at a cognitive (abstract/symbolic) level. These acquired representations can be unidimensional, representing information like spatial position, or multidimensional. Finally, the influence of the different representations probably changes with practice (shift of dominance).

1.6 Brain mechanisms

In the previous section, cognitive models of learning movement sequences were discussed. Cognitive models give an approximation of the processes underlying behavior in order to understand and predict behavior. In contrast, brain models, which will be discussed in the present section, give a description of the brain mechanisms underlying behavior using indices of brain activity too. Evidence for the brain mechanisms underlying discrete sequence learning comes from behavioral, neuroimaging, and neuropsychological studies.

It is often proposed that complex movements are controlled hierarchically (e.g. Gordon & Meyer, 1987; Kornbrot, 1989). Hierarchical control models assert that low level mechanisms are responsible for executing decisions which are made at higher levels. With practice, control can shift from higher to lower order levels in the system. With respect to sequence learning, some studies suggest that the control of familiar, practiced sequences, which are controlled more or less automatically, primarily involves subcortical structures, like the cerebellum and basal ganglia, whereas the control of new sequences is based on cortical structures, (e.g. Ashe, Lungu, Basford, & Lu, 2006).

The prefrontal cortex (see Figure 1.2), which is at the highest level of the cortical hierarchy, is involved in the representation, planning and memory of actions (Fuster, 2001; Koechlin & Jubault, 2006; Ashe et al., 2006; Willingham, 1998), and is highly active during new movement sequences. This structure is no longer active when execution becomes automatic (Jenkins, Brooks, Nixon Frackowiak, & Passingham, 1994). In addition, the posterior parietal cortex (see

Figure 1.2) is important for the coordination of visually presented sequences of movements as it integrates vision, eye position and limb positions (Graziano & Gross, 1998; Andersen & Buneo, 2002). Multiple spatial reference frames are thought to be represented in the parietal cortex, for example visual spatial and action related representations (Colby & Goldberg, 1999), which are probably related to different frames of reference. Thus, when movement execution involves spatial representations, the posterior parietal cortex will be active.
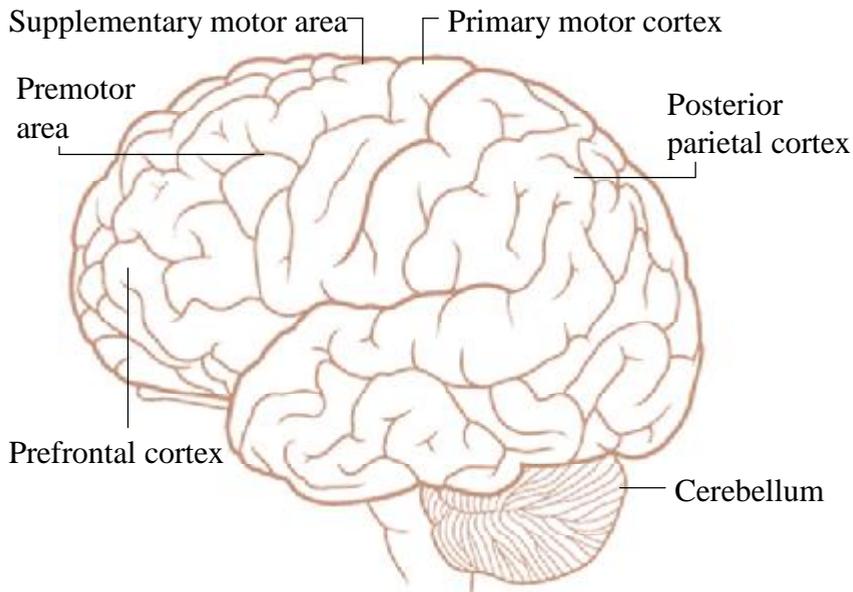
Figure 1.2 Brain areas involved in motoric sequence learning (subtracted from www.BrainConnection.com, © 1999 Scientific Learning Corporation).

The prefrontal and the posterior parietal cortex send information to the premotor area (PMA) and the supplementary motor area (SMA) (see Figure 1.2), which contain more concrete representation (Ashe et al., 2006). The PMA is active during the planning of complex movements based on external cues (the sensory guidance of movement), whereas the SMA is active during the planning of sequences which are under internal control (Shima & Tanji, 1998). The PMA is connected to the cerebellum (see Figure 1.2), which is thought to be important for the timing of rapid movements (Jueptner & Weiller, 1998; Sakai et al., 2000; Ivry, Keele, & Diener, 1998), automatization of skills (Jenkins et al., 1994), the establishment of new motor programs (Ito, 1984), modification of performance

during motor learning (Seidler et al., 2002) and for attention (Courchesne et al., 1994; Ivry & Hazeltine, 1995). In contrast, the SMA is connected to the basal ganglia (including the striatum, globus pallidus, subthalamic nucleus and substantia nigra), which are thought to be important for chunking (Graybiel, 1998), and for inhibiting unwanted movements and thereby selecting correct movements (Brooks, 1995). Thus, in short, it is suggested that the PMA and the cerebellum form a recurrent loop during sensory guided movements, whereas the SMA and the basal ganglia form a recurrent loop during sequences of movements which are under internal control (see Figure 1.3).

In fact, the SMA is often separated in the SMA-proper (from now on called the SMA) and the pre-SMA (which lies anterior to the SMA). The SMA is highly active during the execution of learned sequences and less active during the execution of new sequences (Willingham, 1998; Hikosaka et al., 1999), whereas the pre-SMA is highly active when new sequences are learned and less active when sequence execution becomes automatic (Hikosaka et al., 1996; Miyashita, Hikosaka, Miyashita, Karadi, & Rand, 1997; Sakai et al., 1998). This suggests that with practice, as a motor sequence is learned, activation shifts from the pre-SMA to the SMA. The SMA is thought to play a role in the temporal organization of sequences (Tanji, 1994; Kennerley et al., 2004; Verwey, Lammens, & Van Honk, 2002), the retrieval of a sequence from motor memory (Tanji, 1994; Hikosaka et al., 1996) and in intermanual transfer (Perez, Tanaka, Wise, Willingham, & Cohen, 2008) whereas the pre-SMA is thought to play a role in the temporal organization of new sequences (Kennerley et al., 2004) and in switching between sequences (Shima, Mushiake, Saito, & Tanji, 1996).

The primary motor cortex (M1) (see Figure 1.2), which consists of a somatotopic representation of the different body parts (of which a large part is devoted to hand and finger movements), contains the next level of representation. M1 receives information from the (pre-) SMA and PMA (Ungerleider, Doyon, & Karni, 2002) and is the main source of axons to the spinal cord and therefore responsible for generating the neural impulses to the spinal cord, which controls execution of movement. In addition, after long-term practice, aspects of the sequence of movements become represented in M1 (Matsuzaka, Picard, & Strick, 2007), however, it is unclear at what level.

In summary, M1 generates the neural impulses controlling the execution of movement sequences and with extensive practice represents aspects of the sequence of movements. During initial sequence learning, as movement is based on external cues, sequence execution primarily relies on the PMA and the cerebellum (stimulus-response learning) (Hikosaka et al., 1999; Verwey et al, 2002). With additional practice, as sequence learning becomes under internal control, the temporal organization of the sequence will occur at the level of the pre-

SMA and the basal ganglia (Hikosaka et al., 1999; Verwey et al., 2002). With even more practice, as sequence execution becomes automatic, the prefrontal cortex (higher order organization) and the posterior parietal cortex become less involved (Verwey et al., 2002). Figure 1.3 illustrates the most important connections between brain areas involved in motor sequence learning.
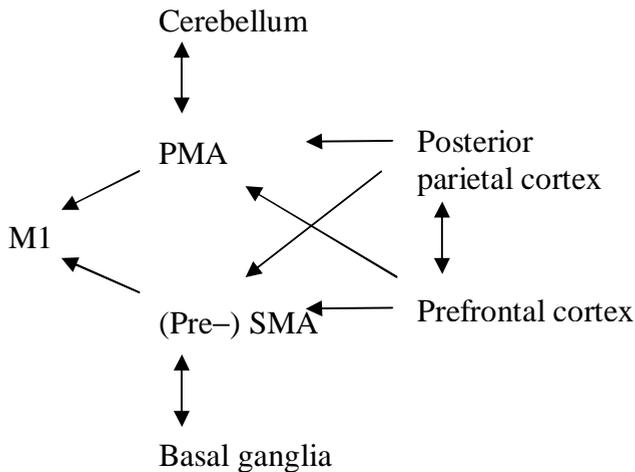
Figure 1.3 A simplified model of the most important connections between the brain areas involved in motor sequence learning.

Based on this simplified model of the most important connections between brain areas involved in motor sequence learning, presented in Figure 1.3, predictions can be made regarding brain mechanisms underlying the discussed models. It suggests that stimulus-response learning, when movements are based on external cues, relies on the PMA and the cerebellum (stimulus-response stage of the model of Verwey (2001) and the model of Hikosaka et al. (1999)). Furthermore, the pre-frontal cortex, the parietal cortex and the pre-SMA are involved during initial practice, as higher order information and spatial information are needed (cognitive processor of the model of Verwey (2001) and the spatial processor of the model of Hikosaka et al. (1999)). With additional practice the SMA and the basal ganglia become involved, as learning becomes under internal control (motor processor of the model of Verwey (2001) and the model of Hikosaka et al. (1999)). Finally, when sequence learning becomes automatic, the prefrontal cortex (higher order organization) and the posterior parietal cortex become less involved and M1 represents aspects of the sequence of movements (Karni, et al., 1998).

1.7 Preparation

Before execution of a sequence of keypresses, this motor sequence can be prepared. The same neural network, depicted in Figure 1.3, is thought to be involved in motor preparation and motor execution (Catalan, Honda, Weeks, Cohen, & Hallett, 1998; Jeannerod, 1994). Studying sequence preparation can therefore provide other important information concerning the processes underlying sequence production, as measures of execution of a sequence are always contaminated with the preparation of the following responses, in line with the idea of parallel processing. Given that preparation is covert, measures derived from the EEG appear especially useful to study movement preparation (e.g. Dirnberger et al., 2000; Van der Lubbe, et al., 2000). Event related potentials (ERPs) are indeed suitable to track the time course of functional processes underlying movement preparation. In the present thesis, we employed the contingent negative variation (CNV), the lateralized readiness potential (LRP), and the contralateral delay activity (CDA) to study preparation of motoric sequences, since they give information about several different aspects of preparation at the level of brain activity.

The CNV is a negative going wave with mostly a central maximum that unfolds in the interval between a warning stimulus and an execution signal (e.g. a go/nogo-signal) (e.g. Jentzsch & Leuthold, 2002). The CNV is thought to reflect general motor preparation and previous studies suggest that the CNV mainly originates from M1 and/or SMA (Cui, et al, 2000; Leuthold, Sommer, & Ulrich, 2004).

In addition, the LRP is related to the readiness potential, which displays greater negativity over the motor cortex contralateral to the responding hand in case of voluntary hand movements. The LRP is computed by averaging the contra-ipsilateral difference waves for left and right responses, thereby eliminating response-unrelated hemispheric asymmetries. This results in a deviation from the baseline before the response with a peak at the moment of the response (De Jong, Wierda, Mulder, & Mulder, 1988; Gratton, Coles, Sirevaag, Eriksen, & Donchin, 1988). The LRP is thought to reflect effector-specific motor preparation (Leuthold & Jentzsch, 2001), and previous studies suggest that the LRP originates from M1 (e.g. Leuthold & Jenzsch, 2002).

Finally, the CDA has been considered as an index for the encoding and/or maintenance of items or locations in visual memory for certain duration (Klaver, Talsma, Wijers, Heinze, & Mulder, 1999; Vogel, McCollough, & Machizawa, 2005). The CDA consists of a contra- minus ipsilateral negativity relative to the relevant stimulus side. The CDA is maximal at posterior recording sites (above visual cortex) and is calculated by subtracting activity at ipsilateral electrode sites from the corresponding contralateral electrode sites. The CDA can probably be used to

assess the demand on visual working memory while preparing fixed keying sequences.

1.8 Dyslexia

The models and mechanisms described in this thesis are applicable to healthy adults. However, to learn more about sequence learning, it is interesting to also study the differences in sequence learning in people with a particular condition, like dyslexia. Some studies suggest that sequence learning (Hari & Renvall, 2001; Howard, Howard, Japikse, & Eden, 2006; Menghini, Hagberg, Caltagirone, Petrosini, & Vicari, 2006, Nicolson, et al., 1999) and chunking (Hari & Renvall, 2001) are impaired in people with dyslexia. Since the DSP task is suitable for studying explicit sequence learning and chunking we questioned if dyslexics have difficulties with the execution of the DSP task. Previous research has primarily focused on the relationship between implicit sequence learning and dyslexia (e.g. Howard, et al., 2006; Menghini, et al., 2006; Rüsseler, Gerth, & Munte, 2006), whereas the relationship between explicit sequence learning and dyslexia has not been examined yet.

Developmental dyslexia (from here on called dyslexia) is defined as a specific impairment in reading abilities, unexplained by any kind of deficit in general intelligence, learning opportunity, general motivation or sensory acuity (Critchley, 1970; World Health Organization, 1993). Dyslexics usually make the following errors: visual confusion of morphologically similar letters (such as b and d), difficulty with the instant identification of a common word and difficulty with the conversion from graphemes to phonemes. In addition to these language-related problems, dyslexics often show deficits in motor coordination, visual processing, skill automatization, the processing of rapid sensory stimuli (Stein & Walsh, 1997; Eden & Zeffiro, 1998; Habib, 2000) and in mental rotation (Rusiak, Lachmann, Jaśkowski, & Van Leeuwen, 2007). However, it remains unclear whether these problems are an additional risk factor to the language-related problems, have a causal form to the language-related problems, or if they are unrelated to the language related problems (Hari & Renvall, 2001). Several theories have been postulated to account for the difficulties associated with dyslexia.

First, the most established theory is the phonological processing theory which suggests that dyslexia is caused by a deficit at the level of the phoneme representation (Paulesu et al., 1996; Brunswick, McCrory, Price, Frith, & Frith, 1999; Temple et al., 2001). This theory describes language related deficits in dyslexia, but it does not explain deficits found in other domains. Previous studies have linked the phonological deficit to a reduction or absence of activity in the left temporoparietal cortex (e.g. Rumsey et al., 1992). This phonological processing

theory is dissatisfying, since this theory does not explain deficits in motor coordination, visual processing, skill automatization, the processing of rapid sensory stimuli and in mental rotation.

Second, the magnocellular theory links dyslexia to a deficit in the magnocellular system, which processes fast visual information (Eden et al., 1996). In addition, some studies suggest that the magnocellular deficit extends to other modalities, in that dyslexics are poor at processing stimuli that incorporate brief, rapidly changing components in the tactile and auditory modality (Tallal, 1980; Tallal, Miller, & Fitch, 1993; Menghini et al., 2006; Stein & Walsh, 1997). This temporal processing theory suggests that the brain of dyslexics is unable to process rapidly changing and rapidly successive stimuli in the auditory and visual modality (Tallal & Piercy, 1973: Tallel, Stark, & Mellits, 1985). Therefore, the temporal processing theory gives a plausible explanation for linguistic, auditory, and visual deficits for dyslexics.

Third, somewhat in line with the temporal processing theory, Nicolson and Fawcett suggest that dyslexics have a deficit related to automatization in all modalities and in all tasks, and thus also in gross and fine motor skills (Nicolson & Fawcett, 1990; Fawcett & Nicolson, 1992). They showed that dyslexics have deficits in postural stability (Fawcett & Nicolson 1999; Fawcett, Nicolson, & Dean, 1996), in the automatization of skills (Nicolson & Fawcett, 1990), in time estimation (Nicolson, Fawcett, & Dean, 1995), in speeded performance (Nicolson & Fawcett, 1994), and in eye blink conditioning (Nicolson, Daum, Schugens, Fawcett, & Schulz, 2002). These automatization deficits are thought to be related to a cerebellar deficit (Nicolson, Fawcett, & Dean, 1995, 2001), for which behavioral, neuroimaging and neuroanatomical evidence was found (Fawcett et al., 1996; Finch, Nicolson, & Fawcett, 2002; Nicolson et al., 1999). This cerebellar deficit hypothesis can be regarded as an alternative to the magnocellular theory or as a parallel mechanism (Nicolson et al., 2001).

Finally, as a link between the magnocellular theory and the impaired processing of rapid stimulus sequences, Hari and Renvall (2001) suggested the sluggish attentional shifting (SAS) hypothesis. The SAS hypothesis suggests that dyslexics cannot easily disengage attention once it is engaged, which results in the prolongation of chunks. This prolongation of chunks impairs the processing of rapid stimulus sequences, and should be seen in all sensory modalities. For example, the prolongation of input chunks can lead to a distorted phonological representation and therefore can cause reading deficits and impaired speech perception. In addition to language related problems, the SAS hypothesis suggests that motor sequencing and chunking is also impaired in dyslexia.

In conclusion, different theories suggest different origins of dyslexia, like a temporoparietal deficit, a magnocellular system deficit or a cerebellar deficit. In

addition, different theories account for different problems in dyslexia, like phonological problems, visual processing problems, skill automatization problems or problems with the processing of rapid sensory stimuli. Given the present thesis, it is interesting that some theories suggest problems with motoric sequence leaning in dyslexia (cerebellar deficit hypothesis and the SAS-hypothesis) and others do not (phonological processing theory and magnocellular theory). The present thesis examined whether people with dyslexia have problems with the execution of explicit motor sequences and with chunking within those sequences. Since the cerebellum is thought to be involved in the stimulus-response stage of sequence learning, it is suggested that, if a cerebellar deficit underlies dyslexia, dyslexics may have difficulties with initial sequence learning. An initial difficulty with sequence learning will also agree with an automatization deficit. In contrast, the SAS-hypothesis predicts that chunking is impaired in dyslexics, which is related to the basal ganglia.

1.9 Outline of the thesis

This thesis will address several aspects of the mechanisms underlying motoric sequence learning. In chapter 2 (De Kleine & Verwey, 2009a), the focus is on the nature of representations underlying skill in the DSP task. The development of effector-specific and effector-unspecific representations during discrete sequence learning was studied and we wondered whether these representations were position-dependent or not, relative to the body. It was predicted that movement sequences are initially learned predominantly in effector-independent spatial coordinates and only after extended practice in effector-dependent coordinates. In this study the hand used and the hand position were manipulated during the DSP task.

In chapter 3 (De Kleine & Van der Lubbe, in preparation-a) we studied whether the different phases of sequence learning were already visible in EEG derivatives during the preparation of sequences. Based on the model of Verwey (2001) and the model of Hikosaka et al. (1999) different hypotheses were proposed regarding the influence of a cognitive and a motor processor on preparation in the DSP task. In this study the preparation of familiar and unfamiliar sequences was compared, and measures derived from the electroencephalogram (EEG) were used to study these covert preparatory processes.

In chapter 4 (De Kleine & Van der Lubbe, in preparation-b) the preparation of familiar, unfamiliar and mirrored sequences (executed with the unpracticed hand) was compared, to give additional information about the format of the effector-independent representation. It was predicted that the same general motor representation underlies mirrored and practiced sequences, but that additional

processes are recruited to perform the transformation. Furthermore, the transfer of segmentation patterns was studied.

In chapter 5 (De Kleine & Verwey, 2009b) and chapter 6 (De Kleine, in preparation) the performance of dyslexics on the DSP task was studied. We examined whether dyslexics had difficulties with the execution of discrete sequences and specifically with the switching between segments. In chapter 5 the execution of sequences consisting of two successive instances of one three-key segment and sequences consisting of two dissimilar instances of a three-key segment were compared. It was predicted that if dyslexics have difficulties with switching between segments, the execution of the sequence without a repetition would be impaired, as a switch between segments had to be made.

The study described in chapter 6 refines the results of the study described in chapter 5, as it investigated the role of practice on the performance of dyslexics in discrete sequence learning. Finally, this thesis concludes, in chapter 7, with a summary and a discussion of the results obtained.

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2 Representations underlying skill in the Discrete Sequence Production task: Effect of Hand Used and Hand Position[*]

Abstract

Various studies suggest that movement sequences are initially learned predominantly in effector-independent spatial coordinates and only after extended practice in effector-dependent coordinates. The present study examined this notion for the discrete sequence production (DSP) task by manipulating the hand used and the position of the hand relative to the body. During sequence learning in Experiment 1, in which sequences were executed by reacting to key-specific cues, hand position appeared important for execution with the practiced but not with the unpracticed hand. In Experiment 2 entire sequences were executed by reacting to one cue. This produced similar results as in Experiment 1. These experiments support the notion that robustness of sequencing skill is based on several codes, one being a representation that is both effector and position dependent.

2.1 Introduction

Most actions we perform in everyday life exist of series of simple movements. For example, we lace our shoes in one fluent movement while it actually consists of a series of several more simple movements. This illustrates that we can sequence simple movements in a specific order to attain fluent execution of more complex movement patterns. Recent research suggests that multiple processors may be active during the execution of a movement sequence and that each processor involves another type of representation that, in addition, develops after varying amounts of practice (Hardy, Mullen, & Jones, 1996; Park & Shea, 2005; Ungerleider, Doyon, & Karni, 2002; Verwey, 2003). For example, skilled movement sequences have been shown to involve spatial and nonspatial information (Bapi, Doya, & Harner, 2000; Koch & Hoffmann, 2000a; Mayr, 1996) as well as effector-dependent and effector-independent components (Hikosaka et al., 1999; Verwey, 2003). It is generally accepted that sequence learning develops through various learning phases, from an initial attentive phase to an automatic phase, in which no attention is needed to perform the movement. This has been described also as a transition from the declarative phase to the procedural phase (Fitts, 1964;

[*] In press with Psychological Research, De Kleine, E. & Verwey, W.B.

Anderson, 1982). For example, without practice full attention is needed to lace a shoe, but after practice the hands seem to know how to execute the task. Yet, evidence for the different representations and their role at various stages of skill remains scattered and people may well be flexible at switching from one to another representation (Verwey, 2003).

Hikosaka et al. (1999) proposed a model in which sequence learning is acquired independently by two parallel systems; one using the spatial system and one using the motor system. The spatial system is assumed to be predominantly active at the early stages of sequence learning and involves knowledge of individual sequence elements in codes that are not effector-dependent. The motor system is assumed to be primarily active at the later stages of sequence learning and movement skill is assumed to involve effector-dependent sequence knowledge. Both systems learn the sequence independently and are assumed to be simultaneously active. However, Hikosaka et al. (1999) propose that the level of system activation varies across practice and either sequence mechanism may have a more important contribution, depending on the behavioral context. An additional feature of their model is that during execution of a movement sequence the motor system can learn from the spatial system and visa versa.

In extension to the Hikosaka et al. (1999) model, Bapi et al. (2000) distinguished an effector-dependent and an effector-independent sequence representation. They suggest that the effector-dependent representation is acquired relatively slowly by the motor system and that the effector-independent representation is in visual/spatial coordinates and acquired relatively fast. In a later study, Bapi, Miyapuram, Graydon, & Doya (2006) provided evidence that different cortical and subcortical networks are engaged at various stages of learning which supported the notion of different sequence representations. The Hikosaka et al. (1999) model suggests that, in what they call the pre-learning stage, each stimulus leads to a movement without any effect of preceding or subsequent stimuli and therefore each movement relies on an individual sensorimotor transformation. However, during repeated execution of movement patterns representations develop that code the order of the individual movements. This would occur for the spatial and for the motor system, resulting in a spatial sequence and a motor sequence. The Hikosaka et al. (1999) model assumes that the spatial sequence is acquired relatively quickly and the motor sequence is acquired more slowly.

In order to differentiate the reliance on different types of sequence representations, Verwey (2003) analyzed response time distributions of a sequence learning task. His analysis of response time distributions was in line with the notion that during practice various processing modes had developed and that participants can switch from one to another processing mode as a function of whether the forthcoming sequence is expected to be familiar. On basis of the

response time distributions, Verwey (2003) distinguished (at least) three processing modes, a fast sequence mode possibly involving sequence learning at the motor level, a moderately fast mode perhaps involving sequence learning at a spatial level, and a slow mode that may well involve reacting to individual key-specific cues. The fast and the moderately fast modes correspond to the two stages of the Hikosaka et al. (1999) model and the slow processing mode corresponds to the pre-learning stage mentioned by Hikosaka et al. (1999). In addition, some processors may simultaneously race to determine which will trigger the next response, but support for parallel racing was limited (Verwey, 2003).

To make the picture more complicated, a distinction has been made between spatial representations with an egocentric (i.e., a body-based reference frame) and allocentric (i.e. a world-based reference frame) representations. Egocentric reference frames may be eye-, hand-, or body-centered (Colby & Goldberg, 1999). Execution of spatial tasks is probably based on a mixture of representations with different reference frames (Adam, Hommel, & Umiltà, 2003; Heuer & Sangals, 1998; Liu, Lungu, Waechter, Willingham, & Ashe, 2007; Deroost, Zeeuws, & Soetens, 2006). It is likely that depending on the task at hand, there are dominant processors and representations, and that with practice the contributions of these processors to sequence execution change.

In conclusion, there is a series of findings now indicating that executing movement sequences involves at least three mechanisms that may contribute simultaneously at advanced skill levels. First, when sequence execution involves responding to key-specific cues and there is no practice, control is entirely external and involves reacting to individual key-specific cues. Second, with limited practice, sequence control is based on effector-independent spatial coordinates, which may involve various representations with different reference frames. Third, with extensive practice, effector-dependent knowledge develops at the motor level. At this stage sequence execution may be based on one processor, but also on a mixture of independent spatial and motor processors that are alternated or racing to trigger responses.

In the present study we wanted to determine whether these various components are susceptible to the spatial location at which the sequence is carried out. The contribution of effector-dependent representations can be assessed by performance with the unpracticed effector. Previous research by Verwey and Wright (2004) provided support for the development of an effector-dependent component and for an effector-independent component during practice in the discrete sequence production (DSP) task. They showed that practiced sequences were performed faster with the practiced hand configuration than with an unpracticed hand configuration, suggesting an effector-dependent component, and that the practiced sequences were performed faster than new sequences with the

unpracticed hand configuration, suggesting an effector-independent component. In a later study, Verwey and Clegg (2005) showed that the effector-dependent component also developed during the serial reaction-time task. They suggest that this effector-dependent component developed as a result of the extended practice they had used in their experiment, which is unusual in the serial reaction-time task. However, these studies did not investigate the contributions of spatial representations to effector-dependent and effector-independent sequence learning. The contribution of the spatial representation can be examined by transferring an acquired sequencing skill from one spatial configuration to another. A study by Grafton, Hazeltine and Ivry (1998) showed that participants, executing the serial reaction-time task, are capable of transferring their skill from a normal to a large keyboard. This suggests that sequence knowledge can be represented at a relatively abstract level, independent of muscles used to respond and independent of the spatial representation. In contrast, a study by Rieger (2004) investigated the spatial representation during skilled typing with crossed hands and showed that typing skill involves a spatial representation. The models of Hikosaka et al. (1999) and Verwey (2003) suggest that effector-independent sequence learning is influenced by spatial coordinates because it is not related to specific body parts, while effector-dependent sequence learning is not influenced by spatial coordinates because it is related to specific body parts. However, to our knowledge this has not yet been investigated.

        In the present study we used the DSP task which is thought to stimulate the development of an effector-dependent component because a discrete sequence of limited length is practiced thoroughly (Verwey & Wright, 2004). In a typical DSP task two discrete sequences are practiced by responding to fixed series of three to six key-specific stimuli. All but the first stimuli are presented immediately after the response to the previous stimulus. In the present study each participant practiced two 7-key DSP sequences with their left hand. In order to test for effector-dependent and effector-independent sequence learning, the hand used to execute the sequence was varied during test phase. In order to examine the role of spatial representations on sequence execution the position of the keyboard on which the participants responded was also varied during the test phase. During the practice phase the keyboard was either placed 90° to the left side of the body or 90° to the right side of the body while the test phase involved both positions. So, during the practice phase participants practiced two sequences with their left hand, with the keyboard either at the left or the right side of their body. The test phase involved a 2 (Hand: practiced/left vs. unpracticed/right) x 2 (Keyboard position: familiar vs. unfamiliar) x 2 (Sequence: familiar vs. random) between blocks design to examine transfer to the unpracticed hand and the unpracticed keyboard position. The independent variable Sequence was only used in Experiment 1.

In addition, the DSP is highly suitable to study sequence segmentation (Rhodes, Bullock, Verwey, Averbeck, & Page, 2004). Previous studies have shown that longer sequences consist of independent segments, which are thought to represent motor chunks (Verwey, 2001; Verwey, Lammens, & Van Honk, 2002). In line with Allport (1980), Schmidt (1988) and Shaffer (1991), Verwey (2001) proposed that a cognitive and a motor component may underlie discrete sequence production. The cognitive component is thought to select a sequence (or chunk), based on a symbolic representation, and this sequence (or chunk) is read and executed by the motor component. The cognitive component additionally plans and organizes the goal structure of movements (Shaffer, 1991). Based on this model it could be suggested that chunk execution is more susceptible to the spatial location at which the sequence is carried out than chunk transition, as chunk execution probably relies on a motoric representation becomes effector-dependent with practice. Therefore additional analyses were performed to investigate the contribution of a spatial representation to the different phases (chunk execution and chunk transition) of sequence execution.

In short, the purpose of the present experiments was to determine the spatial nature of effector-dependent and effector-independent representations at more advanced levels of sequence learning, by varying the hand and the position of the hand, relative to the body. Experiment 2 was conducted to replicate the results of Experiment 1 and to ascertain that the effects found in Experiment 1 had not been caused by different stimulus-response mappings in the two keyboard location conditions. That is, in Experiment 1 every key press was indicated by a cue and changing keyboard position implied a change in stimulus-response mapping too, the possible role of which was excluded in Experiment 2.

Experiment 1

2.2 Method

Participant
Thirty-two students (12 men, 20 women) from the University of Twente served as participants in this experiment. All were right-handed and between 18 and 27 years old. They received course credits for their participation.

Apparatus
Stimulus presentation and response registration were controlled by E-Prime 1.1 on a 2.8 GHz Pentium 4 PC running under Windows XP. Participants were seated in a dimly lit room in front of a computer screen. A chinrest was used to ensure a

constant viewing distance of 45 cm and a fixed head position. The keyboard was positioned in a holder either on a table 90° to the left side of the body, or on a table 90° to the right side of the body, depending on the condition (see Figure 2.1).

Figure 2.1 Illustrations of a participant who executed the sequence with her right hand and the keyboard on the left side of the body (top) and with the keyboard on the right side of the body (bottom).

Task

The display showed four horizontally aligned squares that functioned as placeholders for the stimuli. The squares were 2.8 cm long and wide and there was 0.4 cm between the squares. The four squares were drawn in silver and appeared in the center of the screen on a black background. At the start of a sequence the squares were filled with the background color (black). After a random time interval between 500 and 1000 ms one square was filled with blue or purple, to which the participant reacted by pressing the corresponding key (to facilitate sequence learning two colors were used to differentiate between the two sequences). Immediately after a key press another square was filled, and so on. If a participant pressed a wrong key, an error message was given and the same square was filled

again until the correct response was given. A premature first response was followed by feedback indicating that the response was too early, and the random foreperiod started again. One sequence involved seven successively filled squares and responses. After execution of a sequence the next sequence started, again with the four squares filled with black for a random time interval between 500 and 1000 ms.

Experimental conditions and counterbalancing variables are listed in Table 2.1. In this experiment four sequences were used, vnbnvbc, nvcvncb, bcncbnv, cbvbcvn, which are all characterized by the structure 1232134. Half of the participants (16 participants) were assigned to Group 1 and executed sequences vnbnvbc and nvcvncb, the other half of the participants were assigned to Group 2 and executed sequences bcncbnv and cbvbcvn. In the test phase, participants executed random sequences in addition to the practiced sequences. Executing one sequence was denoted a trial. The random sequences consisted of a random order of seven filled squares, which changed from trial to trial and were made up of the same four stimuli as the practiced sequences. In the random sequences a stimulus was never immediately repeated.

Procedure

During the practice phase the stimuli were arranged in four blocks of 80 sequences (40 repetitions of each sequence), yielding a total of 160 repetitions of each sequence during practice. Halfway through each block there was a break of 20 s, during which the participant could relax. During this break and at the end of each block the participants received feedback about their mean response time and the number of errors since the previous feedback. Every practice block and every two test blocks were followed by a break that lasted approximately as long as a practice block (10 min). Half of the participants in each sequence-group (8 participants) practiced with their left hand on the keyboard on the left side of their body and the other half practiced with their left hand on the keyboard on the right side. In the test phase sequence blocks (practiced-random or random-practice) were counterbalanced across participants.

During practice (and in half the test blocks), participant placed their left little finger on the C-key, their left ring finger on the V-key, their left middle finger on the B-key, and their left index finger on the N-key of a normal computer keyboard. In the remaining blocks of the test phase participants used their right hand, in which case the index finger was on the C-key, the middle finger on the V-key, the ring finger on the B-key and the little finger on the N-key. The four response keys had the same alignment on the keyboard as the four stimulus squares on the display. The instruction was to react as accurately and fast as possible.

Participant	Exp. 1 & 2 Practice Side	Exp. 1 & 2 Sequence	Exp. 1 & 2 Test phase conditions	Exp. 1 Test phase Order
1-4	Left	vnbnvbc, nvcvncb	Lh-Rs, Lh-Ls, Rh-Rs, Rh-Ls	Practice-Random
5-8	Left	vnbnvbc, nvcvncb	Lh-Rs, Lh-Ls, Rh-Rs, Rh-Ls	Random-Practice
9-12	Right	vnbnvbc, nvcvncb	Lh-Rs, Lh-Ls, Rh-Rs, Rh-Ls	Practice-Random
13-16	Right	vnbnvbc, nvcvncb	Lh-Rs, Lh-Ls, Rh-Rs, Rh-Ls	Random-Practice
17-20	Left	bcncbnv, cbvbcvn	Lh-Rs, Lh-Ls, Rh-Rs, Rh-Ls	Practice-Random
21-24	Left	bcncbnv, cbvbcvn	Lh-Rs, Lh-Ls, Rh-Rs, Rh-Ls	Random-Practice
25-28	Right	bcncbnv, cbvbcvn	Lh-Rs, Lh-Ls, Rh-Rs, Rh-Ls	Practice-Random
29-32	Right	bcncbnv, cbvbcvn	Lh-Rs, Lh-Ls, Rh-Rs, Rh-Ls	Random-Practice

Table 2.1 Experimental conditions and counterbalancing variables in Experiment 1 and 2. Lh-Rs = Left hand-right side, Lh-Ls = left hand-left side, Rh-Rs = right hand-right side, and Rh-Ls = right hand-left side. The order of the test phase conditions in Experiment 1 was counterbalanced across participants.

Data analysis

The first two trials of every block, the first two trials after every break, and trials in which one or more errors had been made, were excluded from analyses. Sequences in which the total response time lasted longer than the mean sequence execution time across participants and within blocks plus three standard deviations were also eliminated from the analysis. This last procedure removed 1.1 % of the trials. The Greenhouse-Geisser correction was used with corrected values of the degrees of freedom, when the sphericity assumption of the F-test was violated. Response time (RT) was defined as the time between the onsets of two consecutive keypresses within a sequence (stimulus onset co-occurred with depression of the previous key). The time between onset of the first stimulus and depression of the first key was not included in the analyses, as this stimulus is preceded by an intertrial interval which makes it qualitatively different from the other responses. Mean RTs and arcsine transformed error rates across keys within a sequence were evaluated statistically by analysis of variance (ANOVA) with repeated-measures, with in the practice phase Block (4) and Key (6) as within subject factors, and in the test phase Sequence (practiced vs. random sequence),

Hand (practiced left hand vs. unpracticed right hand), Position (practiced vs. unpracticed) and Key (6) as within subject factors.

2.3 Results

Practice phase
Figure 2.2 shows that participants became faster with practice, $F(3,93)=290.0$, $p<.001$, that some keys were executed faster than others, $F(5,155)=6.6$, $p<.001$. Mean error rate per key press amounted to 2% for the practice phase and some keys produced more errors than others, $F(5,155)=6.7$, $p<.001$. The interaction between Block and Key on RT signified that gradually two segments developed, $F(15,465)=7.1$, $p<.001$. This segmentation was confirmed by planned comparisons that indicated that in block 4 Key 5 was slower than Keys 2,3,4,6 and 7, $Fs(1,31)>10.2$, $ps<.005$. Furthermore, an additional ANOVA also including Group as independent variable showed that there was no significant interaction between Block, Key and Group ($F(15,450)=1.3$, $p>.2$), suggesting that the sequences had been identically segmented across participant groups, despite the two groups practicing different sequences. Summarizing, participants learned the sequences and with practice two segments developed.
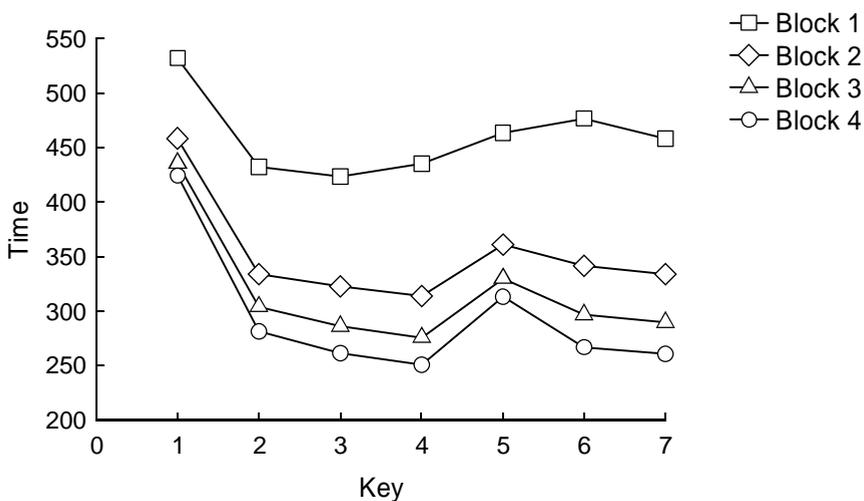

Figure 2.2 Mean initiation time and mean RTs (in ms) across the two sequences in the four practice blocks of Experiment 1 as a function of key position within the sequence.

Test phase

Practiced sequences were executed faster than random sequences, $F(1,31)=219.3$, $p<.001$, and fewer errors were made in practiced sequences (2%) than in random sequences (3%), $F(1,31)=8.6$, $p<.005$. Sequences were executed faster with the practiced (left) hand than with the unpracticed (right) hand, $F(1,31)=7.5$, $p<.01$, and the practiced hand (2%) made less errors than the unpracticed hand (3%), $F(1,31)=8.0$, $p<.01$. The differences in RT between the practiced and the unpracticed hand were bigger during the execution of practiced sequences than during the execution of random sequences, as was shown by the two-way interaction between Sequence and Hand, $F(1,31)=62.4$, $p<.001$. This demonstrated effector-dependent sequence learning.

Sequence execution in the DSP task involves chunking (grouping of information), which results in segments of keys within sequences. Figure 2.3 shows that some keys were executed faster than others, $F(5,155)=12.6$, $p<.001$, and that in the practiced sequence the RT differences between the keys were bigger than in the random sequence, $F(5,155)=9.8$, $p<.001$. Given the obvious segmentation of the practiced sequences, the execution of the practiced sequences during the test phase was analyzed with a 2 (Hand; practiced left hand vs. unpracticed right hand) x 2 (Position; practiced vs. unpracticed position) x 2 (Phase; T5 à transition, T2, T3, T4, T6, T7, à execution) repeated-measures ANOVA on mean RT. Results showed that the transition phase was significantly slower than the execution phase, $F(1,31)=24.7$, $p<.001$. Planned comparisons were performed to investigate the relationship between the two phases and the spatial position. Most importantly, these planned comparisons showed that for the practiced sequences executed with the practiced hand there was a significant difference between the practiced and the unpracticed keyboard position for the execution phase, $F(1,31)=5.6$, $p<.05$, and not for the transition phase, $F(1,31)=0.1$, $p=.98$. Furthermore, the keyboard position did not influence the execution of practiced sequences with the unpracticed hand in either phase, $F(1,31)>0.2$, $p>.3$. Apparently, the unfamiliar position of the practiced hand slowed the execution and not the transition phase of the practiced sequence.

Taken together, the practice phase showed that sequences were learned, became more clearly segmented with practice and that the sequences were identically segmented across participants and sequences. The test phase showed effector-dependent sequence learning. Finally, the position of the practiced hand affected the execution of chunks during effector-dependent sequence learning of the practiced sequences, and not transition.
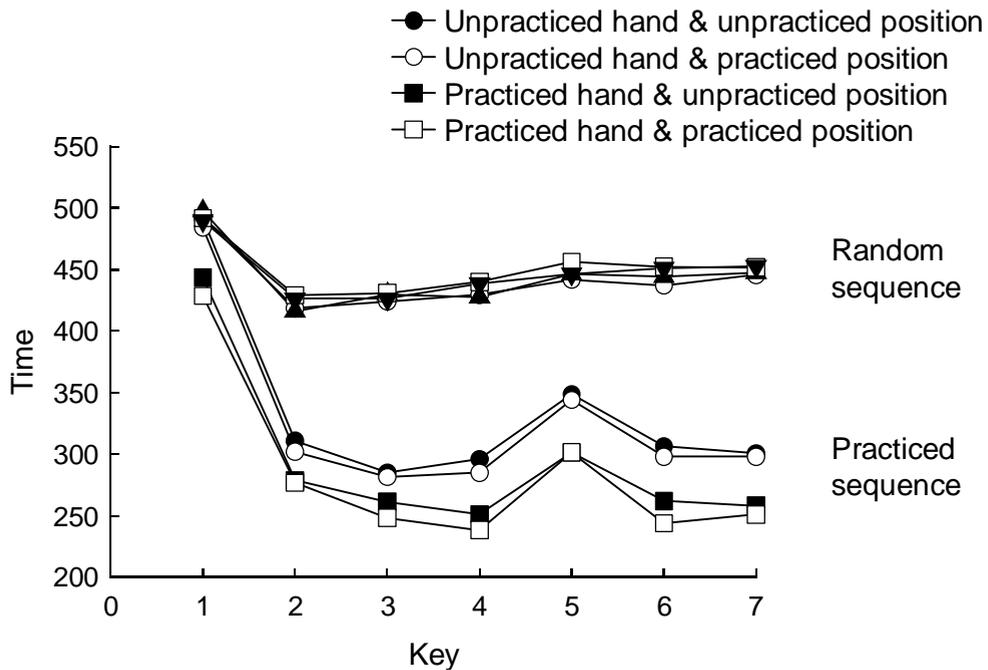
Figure 2.3 Mean initiation time and mean RTs (in ms) in the test phase of Experiment 1 as a function of key position within the sequence, the condition within the test phase, the hand used and the position of the hand used.

2.4 Discussion

The aim of the present study is to examine whether the contribution of effector-dependent and effector-independent representations is influenced by the spatial position of the effector. Previous research suggested that sequences are initially learned in terms of effector-independent spatial coordinates, but later in practice sequences become increasingly effector-dependent (Bapi et al., 2000; Hikosaka et al., 1999; Verwey & Wright, 2004). Our results confirmed that during practice effector-dependent sequence execution developed in that the unpracticed (right) hand was slower than the practiced (left) hand. No effect of spatial position across keys was found on effector-dependent and effector-independent sequence learning.

It turned out that the sequences used in this study were segmented at Key 5. The identical segmentation across sequences and across participant groups could be caused by the regularity imposed by the reversal in keys 2 until 4 (before the beginning of the second segment), as was also found in Koch & Hoffmann (2000b). Other causes are also possible; see Verwey and Eikelboom (2003). Anyway, because of this identical segmentation across participant groups and

sequences two phases of sequence execution could be identified; e.g. chunks transition (T5) and chunk execution (T2, T3, T4, T6 and T7). The results showed that the execution phase during hand dependent sequence execution was influenced by the position of the hand and not the transition phase. This suggests that the elements within a chunk are stored in terms of spatial coordinates, whereas the first element of a chunk is not. Thus, although no effect of the spatial position across keys was found, analyzing the execution and transition phase of chunk independently it showed that the position of the hand influenced the execution of the chunk and not the transition.

A point of consideration is that the comparison of practice vs. random sequences was confounded with a variation in stimulus/response frequencies. The practiced sequences always had 3 keys repeated twice and one original key. The random sequences did not have such regularity; therefore results could have been influenced by this. However, over participants every key had the same amount of repetitions in the practiced sequences. Therefore, we do not think this influenced our results.

Another point of consideration is that stimulus-response mappings varied in the two keyboard positions. For example, executing sequences with the left hand when the keyboard was on the left side of the body resulted in the little finger being closest to the body and the index finger being closest to the computer screen. However, executing sequences with the left hand when the keyboard was on the right side of the body resulted in the little finger being closest to the computer screen and the index finger being closest to body. It could be that the effects found in Experiment 1 were caused by this difference in stimulus-response mappings. Though, no effect of stimulus-response mappings were found in the random condition, therefore it is expected that the stimulus-response mappings were not responsible for the results of the first experiment. Experiment 2 was conducted to ascertain this.

Experiment 2

In this second experiment participants could not automatically react to stimuli because the whole sequence was indicated by one sequence-specific cue. In contrast to Experiment 1 sequences were initially learned verbally, which relies on a limited verbal working memory capacity. If performance in the test phase is independent of stimulus-response mappings, Experiment 2 should replicate the results of Experiment 1.

2.5 Method

Participants
Thirty-two students (13 men, 19 women) from the University of Twente served as participants in this experiment. All were right-handed and between 18 and 26 years old. Participants received course credits for their participation.

Apparatus and task
The apparatus and task used in Experiment 2 were identical to Experiment 1, except that participants memorized two sequences of seven numbers at home before the experiment commenced. At the start of the experiment participants were tested on the memorization of the number-sequences by having them orally report the two sequences. All participants appeared to have correctly memorized the learned sequences. During the experiment the sequences were presented in the same way as in Experiment 1 except that participants reacted with the entire sequence to onset of just the first stimulus. This filled square corresponded with the first number of the learned sequence that had to be pressed and no further key-specific cues were given. For example, if the second square from the left was filled, the sequence that started with a '2' had to be pressed. At the end of a sequence feedback was given about which responses had been wrong (key press 1-7). If all responses had been correct no feedback was given. This time sequences were not distinguished by color of the first stimulus and there were no random sequences in the test phase.

Procedure
The procedure used in Experiment 2 was largely identical to the one in Experiment 1 except that during the first block of the practice phase participants had their sequences, written in numbers on a paper sheet, in front of them, to help them recall the sequences. After the first practice block the written sequences were removed and the participants were to complete the remaining three practice blocks

without them. The instruction to the participants was to react as accurately and fast as possible to the filling of a square by subsequently pressing the appropriate series of keys of the sequence of digits they had learned at home. The mapping of the number to the finger presses was as follows; 1 referred to the left little finger, 2 to the left ring finger, 3 to the left middle finger, 4 to the left index finger, 5 referred to the right index finger, and so on.

Data analysis

The data analysis in Experiment 2 was identical to the data analysis in Experiment 1. The procedure of removing sequences in which the total RT lasted longer than the mean sequence execution time across participants and within blocks plus three standard deviations, removed 1.5 % of the sequences. The data of block 1 of the practice phase of one participant was lost and therefore the calculated means of the first block is based on one participant less than the other block means. Mean RTs and arcsine transformed error rates were evaluated statistically by analysis of variance (ANOVA) with repeated-measures, with in the practice phase Block (4) and Key (6) as within subject factors and in the test phase Hand (practiced left hand vs. unpracticed right hand), Position (practiced vs. unpracticed) and Key (6) as within-subjects factors.

2.6 Results

Practice phase

Figure 2.4 shows that participants became faster with practice, $F(3,90)=165.3$, $p<.001$, and that some keys were executed faster than others, $F(5,150)=12.3$, $p<.001$. Participants made fewer errors in later blocks ($F(3,93)=8.3$, $p<.001$), while more errors were made along the keys within the sequence $F(5,155)=154.9$, $p<.001$). Furthermore, Figure 2.4 shows that in the course of practice the sequences were less clearly segmented into two parts which was signified by the interaction between Block and Key, $F(15,450)=4.5$, $p<.001$. There was also an interaction between Block and Key on errors, $F(15,465)=2.7$, $p<.005$, which was difficult to interpret. Planned comparisons on RT showed that T5 was slower than T2, T3, T4, T6 and T7 separately for Blocks 1 through 4, $Fs(1,31)>6.3$, $ps<.05$. This shows that in this experiment segmentation was already present in the first block of practice. This can be explained by limitations of verbal working memory with limited practice, which did not play a role in Experiment 1. Still, segmentation remained significant until the last block of practice and was of comparable size as in Block 4 of Experiment 1 (difference between Key 5 and the mean of the two adjacent keys in the last practice block was 54 ms in Experiment 1 and 66 ms in Experiment 2). Furthermore, in an additional ANOVA including Group as a

independent variable there was again no significant interaction between Block, Key and Group (F(15,435)=1.0, p=.44) confirming that the sequences were identically segmented over participants, despite the two groups executing two different sequences. Summarizing, participants learned the sequences, which were segmented in two parts.
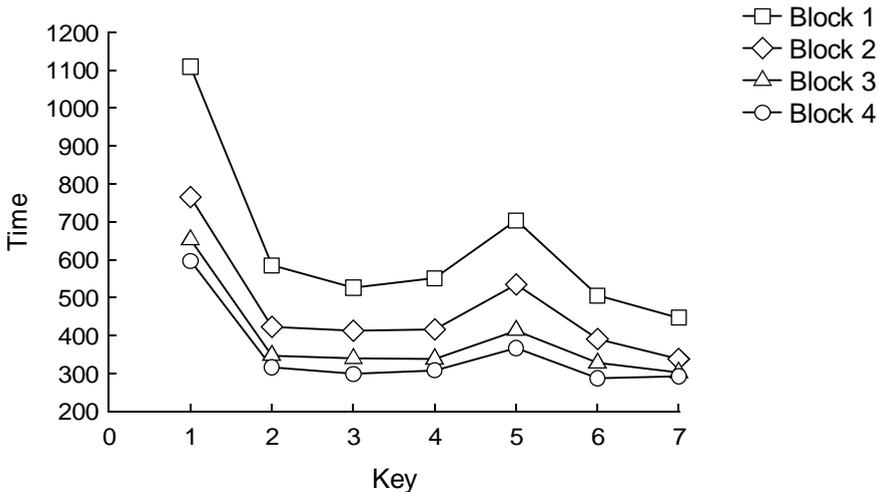
Figure 2.4 Mean initiation time and mean RTs (in ms) in the four practice blocks of Experiment 2 as a function of key position.

Test phase

Participants were faster when executing sequences with the practiced hand than with the unpracticed hand, F(1,31)=63.3, p<.001, and fewer errors were made with the practiced hand than with the unpracticed hand, F(1,31)=14.0, p<..001 (6% vs. 9%).

Figure 2.5 shows that some keys were executed faster than others, F(5,155)=8.8, p<.001.In addition, later keypresses had more errors, F(5,155)=112.5, p<.001. Given the obvious segmentation of the sequences, RTs were analyzed with a 2 (Hand; practiced left hand vs. unpracticed right hand) x 2 (Position; practiced vs. unpracticed position) x 2 (Phase; T2, T3, T4, T6, T7, à execution, T5 à transition) x 2 (Group; sequence vnbnvbc and nvcvncb vs. sequence bcncbnv and cbvbcvn) repeated-measures ANOVA. The transition phase was significantly slower than the execution phase, F(1,31)=31.4, p<.001, and there was an interaction between Hand and Phase, F(1,30)=4.3, p<.05. Planned comparisons showed that the practiced hand was faster than the unpracticed hand in both phases, Fs(1,31)>28.9, ps<.001. The difference in

execution rate between the hands was 82 ms for the transition phase and 55 ms for the execution phase. Further planned comparisons were performed to investigate the relationship between the two phases and the keyboard position. Most importantly, for the practiced sequences executed with the practiced hand there was a significant difference between the practiced and the unpracticed hand position for the execution phase, $F(1,31)=16.1$, $p<.001$, and not for the transition phase $F(1,31)=1.1$, $p>.3$. Furthermore, the keyboard position did not influence the unpracticed hand in either phase, $F(1,31)>0.02$, $p>.5$. See Figure 2.5. Thus, only when using the practiced hand the position of the hand influenced the execution phase of the practiced sequences, but not the transition phase.

Taken together, the practice phase showed that the practiced sequences were learned and identically segmented across participants and sequences. The test phase showed effector-dependent sequence learning and that the position of the practiced hand affected the execution of chunks during effector-dependent sequence learning of the practiced sequences, and not transition.
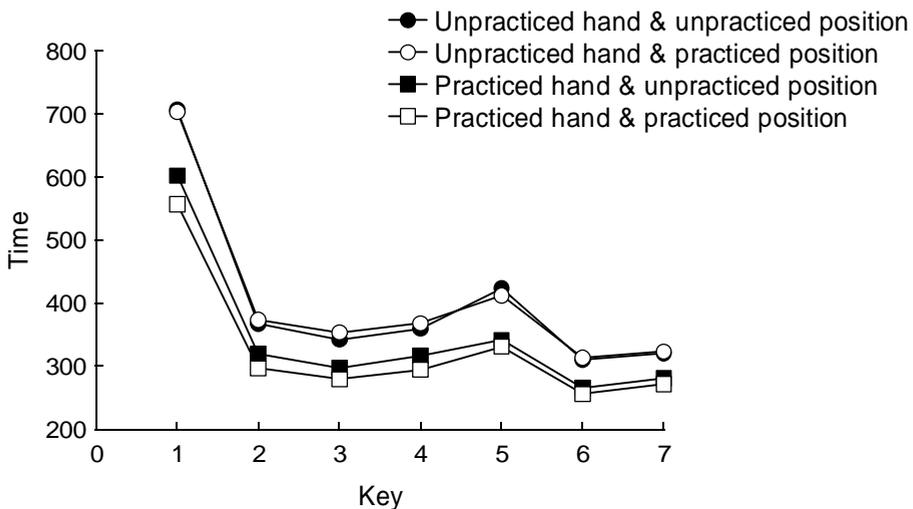
Figure 2.5 Mean initiation time and mean RTs (in ms) in the test phase of Experiment 2 as a function of key position within the sequence, the hand used and the position of the hand used.

2.7 Discussion

The rationale for this second experiment was to replicate the results of the first experiment and to ascertain that the effects found in Experiment 1 had not been caused by different stimulus-response mappings in the two keyboard location

conditions. The question remained; is sequence execution at more advanced levels of practice influenced by the hand used and by the position of the hand used? The initial way in which the sequences had been learned did not influence the eventual performance, thus refuting a stimulus-response mapping explanation for the results of Experiment 1. However, RTs during the first practice block in Experiment 2 were about 150 ms larger compared with RTs during the first block in Experiment 1. This is probably caused by the need to retrieve each key press from verbal memory and translate it one by one.

While no effect of spatial position across keys on effector-dependent and effector-independent sequence learning was found, we do find an effect of spatial position on the execution phase of effector-dependent sequence learning. This indicates again that effector-dependent sequence knowledge includes both a location dependent (execution) and a location independent component (transition).

2.8 General Discussion

In two experiments the influence of the position of the practiced and the unpracticed hand on DSP task performance was examined. In Experiment 1 participants learned the sequences by reacting to key-specific cues and in Experiment 2 participants learned the sequences by translating a numerical code. This difference left the eventual results unchanged, indicating that the effects found in Experiment 1 can not be explained by different stimulus-response mappings in the two keyboard location conditions and that representations that develop during practice with the DSP task are independent of the initial way of learning.

In both experiments participants executed the practiced sequences faster with the practiced than with the unpracticed hand, indicating that participants developed effector-dependent learning of the practiced sequences. This is in agreement with Hikosaka et al. (1999) who argued that at more advanced levels of learning sequences are executed increasingly effector-dependent. Furthermore, the models of Hikosaka et al. (1999) and Verwey (2003) suggest that effector-independent sequence learning is influenced by spatial coordinates because it is not related to specific body parts, while effector-dependent sequence learning is not influenced by spatial coordinates because it is related to specific body parts. However, in both experiments no effect of position across keys was found on effector-dependent or effector-independent sequence learning.

Still, the obvious segmentation of the sequences gave us the opportunity to investigate the influence of the position of the hand on the different phases of sequence execution. It appeared that chunk execution of effector-dependent sequence learning was affected by the spatial position of the hand, while chunk transition was not. This suggests that slowing at T5 was indeed caused by other

processes such as switching to a next chunk. So, the present experiments support the notion that at advanced skill levels sequence execution is based on several representations simultaneously, one being a representation that is both effector and position dependent and one being more general which is both effector and position independent. Furthermore, the present experiment suggests that chunk execution and chunk transition are represented by different codings, as only chunk execution was effected by the spatial position of the practiced hand. This agrees with the view that sequences are represented by different codings (Harrington et al., 2000; Hikosaka et al., 1999; Verwey, 2003; Deroost et al., 2006).

Practice related shifts in representations are also mentioned in other studies. Hoffmann & Koch (1997) and Koch (2007) suggest that with practice sequence learning shift from a stimulus-based representation to a response-based representation. This suggests that the representation that is effector and position independent is stimulus based, while the effector and position dependent representation is response based.

Finally, the present findings suggest that chunk execution of effector-dependent learning is in a body-centred (i.e. trunk, shoulder- or head-centred) reference frame, while chunk transition of effector-dependent learning and effector-independent learning were probably not in a body-centred reference frame and perhaps in a world-based reference frame.

In conclusion, we argue that sequences can initially be learned either verbally or by responding to cues and that with additional practice an effector-dependent (perhaps motor) component develops in parallel to an effector-independent (perhaps spatial) component. We suggest that effector-dependent sequence learning consists of a location dependent component (chunk execution) and a location independent component (chunk transition).

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3 Decreased load on general motor preparation and visual working memory while preparing familiar as compared to unfamiliar movement sequences[*]

Abstract

Learning movement sequences develops from an initial controlled attentive phase to a more automatic inattentive phase. Furthermore, execution of sequences becomes faster with practice, which may result from changes at a central rather than at a peripheral processing level. We examined whether these changes are already present during preparation. Fixed series of six keypresses, familiar or unfamiliar, had to be prepared and executed/withheld after a go/nogo-signal. Results showed an increased demand on general motor preparation and visual-working memory before unfamiliar sequences, relative to familiar sequences. Source localization showed that general motor preparation originated from primary and/or premotor cortex, suggesting a close link between general and effector-specific motor preparation, and that the difference between familiar and unfamiliar sequences originated from posterior sites, probably reflecting visual-working memory.

3.1 Introduction

Piano playing requires the accurate coordination of finger movements on both hands. Each finger movement has to be sequenced in the right order and executed with the right pace relative to finger movements on the same or the other hand. Skilled piano players can rapidly sequence these movements in case of playing a familiar piece, however, in case of an unfamiliar piece, their movements become slower, less precise and seem to require more attention (Drake & Palmer, 2000; Lotze, Scheler, Tan, Braun, & Birbaumer, 2003). Previous studies suggest that different processes underlie the execution of familiar as compared to unfamiliar sequences of movements (e.g. Ivry, 1996; Verwey, 2001; Hikosaka et al., 1999). These processes can be studied by using so-called discrete movement sequences, which are relatively short sequences of movements usually consisting of three up to six keypresses with a clear start- and endpoint. The learning of these sequences

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[*] In Preparation−a, De Kleine, E. & Van der Lubbe, R.H.J.

has been described in several models, and is indeed thought to develop from an initial controlled attentive phase to a secondary automatic phase in which attention is no longer needed (e.g., Cohen, Ivry, & Keele, 1990; Doyon & Benali, 2005; Verwey, 2001). In our study, we examined whether these different processes underlying the execution of familiar and unfamiliar sequences of movements are already active while preparing these movements, by focusing on several measures derived from the electroencephalogram (EEG).

In line with Allport (1980), Schmidt (1988) and Shaffer (1991), Verwey (2001) proposed that a cognitive and a motor processor underlie performance in tasks in which discrete motor sequences are produced. The cognitive processor is thought to initially select a representation of a sequence, based on a symbolic representation, and subsequently this sequence is read and executed by the motor processor. The cognitive processor is additionally involved in planning and organizing the goal structure of movements (Shaffer, 1991). According to this model, the difference between familiar and unfamiliar sequences only concerns the demand on this cognitive processor, which reduces when the load on planning and organization diminishes. Consequently, with familiar sequences this demand will be low, because integrated and complex parts of a sequence (i.e. motor chunks) can be selected at once, using stimulus-response selection rules in working memory. With unfamiliar sequences, however, the demand on this cognitive processor will be high, because each element in the sequence has to be selected separately. Subsequently, the motor chunk or separate elements can be loaded into the motor buffer, after which the sequence can be executed. This loading of the motor buffer and executing of the sequence is thought to be independent of learning, so the demand on the motor processor should be the same for familiar and unfamiliar sequences. With regard to the cognitive processor, no further details were given. For example, it is unclear whether the symbolic sequence representation has a spatial format or a more abstract, lexical format.

Another relevant model for tasks in which discrete motor sequences are produced was proposed by Hikosaka et al. (1999). They proposed that when a sequence is encountered for the first time during a pre-learning stage, every single stimulus is translated into a single response. During practice, sequences are represented in parallel on a spatial and at a motor level. The processor at a spatial level, which is effector unspecific, is thought to be most active during the initial stages of learning, whereas the processor at a motor level is most pronounced during later stages of learning and is thought to be effector specific. The spatial processor of the model of Hikosaka et al. (1999) can be considered to be more specific than the cognitive processor of the model of Verwey (2001), as its format is specified. Furthermore, if we compare the two models with regard to sequence learning, then it appears that the model of Verwey (2001) predicts that learning

only coincides with a decrease in demand on the cognitive processor, whereas the demand on the motor processor remains the same. The model of Hikosaka et al. (1999), however, predicts that sequence learning coincides with a decreased demand on the cognitive processor, and an increased demand on the motor processor.

Sequence learning can be studied by using the discrete sequence production (DSP) paradigm. In a typical DSP task discrete sequences are practiced by responding to series of three to six key-specific stimuli. All stimuli, apart from the first stimulus, are presented immediately after the response to a previous stimulus. In this task, anticipation and programming of the next motor response may already start while executing the previous response (Eimer, Goschke, Schlaghecken, & Stürmer, 1996). In other words, motor preparation and motor execution occur in parallel in this task, which implies that it is difficult to discern the precise function of these processes. In order to get a more clear view on the precise function of the processes underlying familiar and unfamiliar sequences it may be better to separate motor preparation from motor execution. Therefore a modified version of the DSP-task was used, inspired by the precuing paradigm of Rosenbaum, which allows us to study the preparation of movement sequences in isolation from motor execution.

Rosenbaum (1980) designed a paradigm that enables the separation of motor preparation from execution by using precues (often denoted as S1) that provide specific information about the forthcoming movement. For example, the precue indicates the response hand, response finger, response force and/or the direction of the forthcoming movement (Ulrich, Leuthold, & Sommer, 1998). After a delay period an execution/withhold (go/nogo) signal (S2) is presented, which may additionally provide missing information about the forthcoming movement in case of partial or non-informative precues. Results show that participants can use this advance information for response preparation, as RT decreased with informative precues as compared to non-informative precues (e.g. see Leuthold & Jentzsch, 2002a). This decrease depends on the number and the type of precued movement dimensions, suggesting that several movement parameters can be prepared in parallel. Similar to the S1-S2 paradigm of Rosenbaum, a go/nogo version of the DSP task was designed in which six key-specific stimuli were subsequently presented, which after a preparatory interval were followed by a go/nogo-signal. In case of a go-signal, participants were to react as fast and accurately as possible by pressing the six corresponding keys in the indicated order, and in case of a nogo-signal responses should be withheld. This modified DSP task allowed us to study the preparation phase of sequence learning in isolation from motor execution.

To study movement preparation in these paradigms, measures derived from the EEG appear especially useful (Dirnberger et al., 2000; Van der Lubbe,

Wauschkuhn, Wascher, Niehoff, Kömpf, & Verleger, 2000; Verleger, Wauschkuhn, Van der Lubbe, Jaśkowski, & Trillenberg, 2000b). Event related potentials (ERPs) are indeed suitable to track the time course of functional processes underlying movement preparation. In the present study, we employed the contingent negative variation (CNV), the lateralized readiness potential (LRP), and the contralateral delay activity (CDA) to study preparation of motoric sequences, since they give information about several different aspects of preparation.

      The CNV is a negative going wave with mostly a central maximum that unfolds in the interval between a warning stimulus and an execution signal (e.g. a go/nogo-signal) (Jentzsch & Leuthold, 2002; Verleger, Vollmer, Wauschkuhn, Van der Lubbe, & Wascher, 2000a). The interpretation of the late, centroparietally distributed part of the CNV varies. First, Verleger et al. (2000b) suggested that the late CNV represents the binding of awaited stimuli (S2) to their required responses, as stimulus-response binding was thought to be more important in an S1-S2 paradigm than pure motor preparation. Second, Brunia (2001), and Ruchkin, Johnson, Grafman, Caoune, and Ritter (1996) revealed that non-motoric processes such as stimulus anticipation and visuospatial working memory also contribute to the late CNV. Finally, Cui et al. (2000) suggested that the late CNV reflects the level of preprogramming, consisting of the processes that specify the task to be performed and how to perform this task. An increased late CNV for complex movements as compared with simple movements was obtained, which suggests that more preprogramming is taking place before complex movements compared with simple movements. In line with this, Jentzsch, Leuthold, and Ridderinkhof,(2004) and Wild-Wall, Sangals, Sommer, and Leuthold (2003) revealed that with more advance information before an upcoming movement the amplitude of the late CNV increases, which may reflect more preprogramming. The latter results corresponds with the view that the CNV reflects activity of a cognitive processor that is loaded more heavily when more information about the required movements is provided, in line with the sequence learning models of Verwey (2001) and Hikosaka et al. (1999).

      A second ERP measure that can be derived from the EEG is the LRP. The LRP is related to the readiness potential, which displays greater negativity over the motor cortex contralateral to the responding hand. The LRP is computed by averaging the contra-ipsilateral difference waves for left and right responses, thereby eliminating response-unrelated hemispheric asymmetries. This results in a deviation from baseline before the response with a peak at the moment of response (De Jong, Wierda, Mulder, & Mulder, 1988; Gratton, Coles, Sirevaag, Eriksen, & Donchin, 1988). Verleger et al. (2000a) could distinguish between three lateralized components; an early anterior contralateral negativity (L-400), a contralateral negativity before S2 (preparation related LRP) and a contralateral

negativity beginning at movement onset (motor LRP). The L-400 is thought to originate from the premotor cortex and reflect the encoding of spatial properties of S1 (Verleger et al., 2000a). Furthermore, source localization and magnetoencephalography studies showed that the LRP reflects activity in the primary motor cortex (M1) (Böcker, Brunia, & Cluitmans, 1994a, b; Praamstra, Schmitz, Freund, & Schnitzler, 1999). In addition, Brunia (1980) showed that preparation of hand and foot movements generated LRPs with opposite polarities, suggesting that activity originated from M1, since the foot is represented at the medial site of M1 and the hand at the top of M1. Furthermore, Carrillo-de-la-Peña, Galdo-Álvarez and Lastra-Barreira (2008) suggest that this opposite polarity of the preparation related LRP excludes activity in secondary motor areas, like SMA and premotor cortex, as foot and finger movements are both represented at the same site in these areas. In the present study we mainly focused on the preparation related LRP, which is thought to originate from M1 and reflect effector specific motor preparation (Leuthold & Jentzsch, 2001).

Another useful lateralized ERP measure is the contralateral delay activity (CDA) (or in case of brief negativity the posterior contralateral negativity (PCN)), which may be considered as an index for the encoding and/or maintenance of items or locations in visual memory for a certain duration (Klaver, Talsma, Wijers, Heinze, & Mulder, 1999; Vogel, McCollough, & Machizawa, 2005). The CDA consists of a contra- minus ipsilateral negativity relative to the relevant stimulus side. The CDA is maximal at posterior recording sites (PO7 and PO8) and is calculated by subtracting activity at ipsilateral electrode sites from the corresponding contralateral electrode sites. Most studies use bilateral stimuli in order to keep stimulation of both hemifields as comparable as possible. In short, the amplitude of the CDA can be used as an index for the load on visual-working memory.

In the present study, we examined whether differences between familiar and unfamiliar sequences are already present while preparing these sequences. We predicted familiar motor sequences to be executed faster and with fewer errors than unfamiliar motor sequences. According to the model of Verwey (2001) a cognitive processor is more active in case of unfamiliar sequences than in case of familiar sequences whereas activity of the motor processor is thought to be comparable for familiar and unfamiliar sequences. Since the CNV may be considered as an unspecific preparatory index and the LRP is thought to reflect effector-specific motor preparation, this may be reflected in an enlarged CNV while preparing unfamiliar as compared to familiar sequences and no LRP amplitude differences between familiar and unfamiliar sequences. In contrast, based on the model of Hikosaka et al. (1999) the motor processor would be most active during familiar sequences whereas the cognitive processor would be most active during

unfamiliar sequences. This may be reflected in a larger LRP while preparing familiar as compared to unfamiliar sequences and a larger CNV while preparing unfamiliar as compared to familiar sequences. Furthermore, if sequence learning indeed develops from an attentive to an automatic phase and involves visual-working memory, then the CDA would be most pronounced while preparing unfamiliar as compared to familiar sequence. Finally, the CNV, LRP and CDA were expected to be most pronounced just before the go/nogo-signal.

3.2 Methods

Participants
Sixteen students (7 males, 9 females), aged 18-24 years (mean: 21 years) from the University of Twente served as participants. They had a mean handedness score of 20 (range: 13-24), measured by the Annett Handedness Inventory (Annett, 1970), signifying that all participants can be considered as right-handed (1 to 12 indicates left-handed, 13 to 24 indicates right-handed). All participants gave their written informed consent and reported normal or corrected-to-normal vision. Participants were paid € 42 for their participation of maximally 7 hours divided over two days. The study was approved by the local ethics committee of the Faculty of Behavioral Sciences of the University of Twente and was performed in line with the Declaration of Helsinki.

Stimuli and Task
Participants placed their little finger, ring finger, middle finger and index finger of their left and right hand respectively on the a, s, d, f keys and the ;, l, k, j keys. A trial consisted of the presentation of six stimuli and, in case of a subsequent go stimulus, was to be followed by the execution of six spatially corresponding keypresses (one sequence). The presentation of the stimuli is displayed in Figure 3.1. Each trial started with the presentation of a fixation-plus (1.3°) in the center of the screen accompanied with eight horizontally aligned squares (2.5°), four on the left and four on the right side of the fixation-plus (default screen). The alignment of the eight stimulus squares had a total visual angle of 26.5° and corresponded with the alignment of the eight response keys. The eight squares and the fixation-plus were drawn with a silver color line on a black background. 1000 ms after onset of the default screen, one square was filled yellow for 750 ms, next a second square, and so on until a sixth square was filled. Next, the default screen remained for another 1500 ms. Subsequently, the fixation-plus was colored either red (8%) or blue (92%). The red fixation-plus stayed on the screen for 3000 ms and indicated that no action should be executed (a nogo trial) whereas the blue fixation-plus

(presented for 100 ms) indicated that participants had to press the buttons corresponding to the presented sequence of yellow squares (a go trial). Participants were instructed to respond as fast and accurately as possible, and were requested to keep their eyes on the fixation-plus from the moment when the last stimulus disappeared until the final response of the sequence was executed. Feedback was given after the end of a response sequence, but only when a participant reacted before the go/nogo-signal, or when a false button press was conducted.
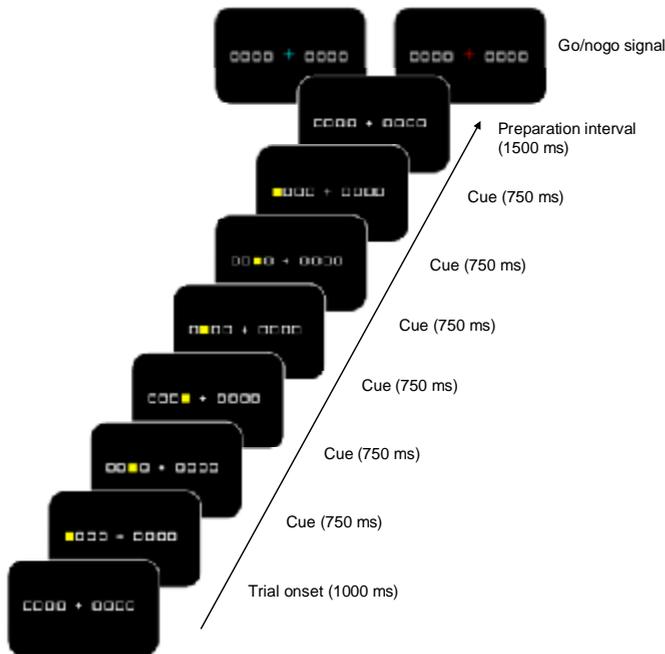
Figure 3.1 An example of the sequence of stimuli from the start of a trial until the go/nogo-signal. The duration of each stimulus frame is indicated along the time axis.

In the present experiment, participants executed eight familiar sequences during the learning phase, which were presented in random order. Every participant practiced four sequences with the left hand and four sequences with the right hand, which were mirror versions(aà;, sàl, dàk, fàj). This was done to reduce differences between left and right hand responses to make calculation of the LRP neater. In order to counterbalance across participants and across fingers four different structures of sequences were used; 134231, 142413, 124314, and 132314. With each structure four sequences were created by assigning different

keys to the numbers, thereby eliminating finger-specific effects. The first structure leads to the sequences adfsda, sfadfs, dasfad, and fsdasf, and so on for the three other structures. The four sequences of each hand started with a different key press and at the same time the four sequences had a different structure. This led to four different versions of sequences, which were counterbalanced across participants. During the test phase eight unfamiliar sequences were added, which resulted in the random presentation of eight familiar and eight unfamiliar sequences. Half of the sequences were carried out with the left hand and the other half with the right hand, equally divided across blocks. Sequences performed with the right hand were again mirror versions of the sequences executed by the left hand. The four versions were counterbalanced across the test phase and practice phase in such a way that the unfamiliar sequences of one group were the familiar sequences of another group. Thus, differences between familiar and unfamiliar sequence cannot be ascribed to the specific sequence employed or to finger-specific effects.

Procedure

Participants were tested on two successive days. On the first day, they performed six practice blocks and on the second day they started with one practice block and subsequently three identical test blocks. During the test blocks EEG was recorded, which implied a break of approximately 90 minutes between the last practice block and the first test block, as the EEG electrodes had to be applied. Participants were instructed to execute the required sequence as fast and accurately as possible after onset of the go-signal. During the practice phase stimuli were arranged in seven blocks of 104 sequences (12 repetitions of each sequence and eight no-go trials), yielding 84 repetitions for each sequence in the practice phase. Halfway each block, a pause of 20 sec was provided in which the participant could relax. During this break and at the end of each block the participants received feedback on the amount of errors and their mean response time. A test block consisted of 104 sequences (six repetitions of each sequence and eight no-go trials) in which familiar and unfamiliar sequences were randomly intermixed. Every block was followed by a small break of approximately 2 minutes and every other block was followed by a break of approximately 10 minutes.

Recording and data processing

The experiment was run on a personal computer (Pentium 4) with a QWERTY keyboard. Stimulus presentation, response registration and production of external triggers were controlled by E-Prime, version 1.1. A 16 inch monitor was placed in front of the participants at a distance of about 45 cm. EEG and electro-oculogram (EOG) were amplified with a Quick-Amp amplifier (72 channels, DC) and recorded

with Brain Vision Recorder (version 1.05) software. EEG was recorded from 61 Ag/AgCl ring electrodes located at standard electrode positions of the extended 10/20 system. An online average reference was employed. EOG was recorded bipolarly, both vertically from above and below the left eye and horizontally from the outer canthi of both eyes. Electrode impedance was kept below 5 kΩ. The EEG and EOG data were sampled at a rate of 500 Hz. Measured activity was digitally filtered online (low-pass 140Hz, DC).

Data analysis

For statistical analyses, Greenhouse-Geisser epsilon correction for the degrees of freedom was applied whenever appropriate. One participant was left out from the final analyses because of the large number of errors (61% correct keypresses, while all other participants had a percentage of correct keypresses of 85% or higher), which suggested that this participant did not fully comply with the task instructions. Furthermore, EEG analyses were performed on all data without artifacts, because elimination of all trials with a single incorrect response would unnecessarily reduce the total number of EEG trials and might additionally introduce a bias for familiar vs. unfamiliar sequences.

The interval between the off-set of the last stimulus and the go/nogo-signal was 1500 ms. The data was segmented starting 1600 ms before the go/nogo-signal until 100 ms after the go/nogo-signal. A baseline was set 1600-1500 ms before the go/nogo-signal. The last stimulus remained present on the screen until the end of the baseline. Trials with artifacts (an amplitude difference larger than 100μV within 50 ms) and out of range values (values larger than +/- 250 μV for prefrontal electrodes, +/- 200 μV for frontal electrodes, +/- 150 μV for central electrodes, and +/- 100 μV for parietal electrodes) were excluded from further analyses (comparable to Van der Lubbe, Neggers, Verleger, & Kenemans, 2006). Next, EEG was corrected for EOG artifacts by the Gratton, Coles and Donchin (1983) procedure. Finally, a low-pass filter with a cut-off at 16 Hz was applied to average event-related brain potentials of individual participants.

Response parameters

Response time (RT) was defined as the time between onset of the go-signal and depression of the first key and as the time between the onsets of two consecutive keypresses within a sequence. The first two trials of every block and after every break and trials with errors were excluded from RT analyses. Trials in which the total RT, the sum of all RTs in one sequence, deviated more than 3 SD from the overall mean total RT per block across participants were additionally eliminated from the RT analysis. This procedure removed 1.4% of the trials. The Percentage Correct (PC) was calculated as the percentage correct key-presses. The mean

RTs and mean PC were evaluated statistically by analysis of variance (ANOVA) with repeated-measures, with in the practice phase Block (7), Key (6) and Hand (2) as within subject factors and in the test phase Block (3), Key (6), Hand (2) and Familiarity (2: familiar or unfamiliar sequence) as within-subjects factors.

EEG parameters

The CNV was computed by averaging EEGs for all trials without artifacts from Fz, Cz and Pz, as these electrodes represent the predominant distribution of the CNV (Leuthold & Jentzsch, 2002b). The LRP and CDA were determined by application of the double subtraction technique to obtain the contralateral minus ipsilateral difference to the response/stimulus side. As a consequence, more negativity at the site contralateral to the required response/stimulus than ipsilateral results in a negative difference wave. Averaged activity was determined in 200ms intervals from -1200 to the go/nogo-signal on which statistical analyses were performed. All analyses included the factors Time Interval (6) and Familiarity (familiar or unfamiliar). The CNV analyses additionally included the factors Hand (2) and Posterior-anterior axis (3). To exclude a confound in terms of volume conduction from C3/4 to PO7/8 electrodes or vice versa for the LRP and CDA, we performed analyses in which these electrodes were treated as a covariate (for a comparable procedure see Van der Lubbe & Woestenburg, 1999).

To facilitate interpretation of the CNV, LRP and CDA, source analyses were performed to specify the likely brain regions accounting for CNV, LRP and CDA activity respectively. The Brain Electricity Source Algorithm (BESA, version 5.1.6) was employed to determine so-called regional sources, which can be regarded as complex sources describing each activity in three orthogonal directions. BESA determines the location and orientation of regional sources by calculating the scalp distribution for a given model and comparing it with the original distribution. The model is optimized by minimizing the residual variance (RV) between the model and the original distribution. Determination of the time windows for the fitting procedure (see Results) were based on inspection of the global field power (GFP: the sum of squares of activity over all channels) of the grand averages, and was chosen from onset of a peak in the GFP to its maximum. Furthermore, determination of the number of sources was based on inspection of the principal component analyses (PCA).

3.3 Results

Behavioral measures

Practice phase

RTs and Percentage Correct (PC) as a function of Block and Hand are compiled in Table 3.1. Responses were faster with the right than with the left hand, $F(1,14)=10.1$, $p=0.007$, participants became faster with practice, $F(6,84)=63.5$, $\varepsilon=0.35$, $p<0.001$, and there was an effect of Key, $F(5,70)=15.6$, $\varepsilon=0.41$, $p<0.001$ (mean RT for Key 1 to Key 6, respectively 454.9, 319.2, 356.4, 348.0, 358.0 and 251.5). Furthermore, the difference in RT between keys decreased with practice, as was shown by the significant interaction between Block and Key, $F(30,420)=2.8$, $p<0.008$.

More correct responses were made with practice, $F(6,84)=26.8$, $\varepsilon=0.28$, $p<0.001$, and there was an effect of Key, $F(5,70)=15.1$, $\varepsilon=0.35$, $p<0.001$ (mean PC for Key 1 to Key 6, respectively 93.3, 92.1, 89.9, 86.8, 84.7 and 87.3). Furthermore, the increase in the number of correct responses differed between keys, as was shown by the interaction between Block and Key, $F(30,420)=5.0$, $p<0.001$. In sum, participants became faster and made more correct responses during the practice phase, which indicates that the sequences were learned.

	Hand	Sequence	Practice phase	Test phase		
				Block 1	Block 2	Block 3
RT	Left	Familiar	342	289	280	280
		Unfamiliar		355	312	299
	Right	Familiar	329	287	278	262
		Unfamiliar		336	313	298
PC	Left	Familiar	91.1	94.4	95.7	96.7
		Unfamiliar		85.0	89.2	89.7
	Right	Familiar	90.8	93.9	94.6	93.7
		Unfamiliar		84.2	89.4	90.3

Table 3.1 Mean RTs (in ms) and PC (in %) as a function of Hand and Sequence for the practice and the test phase.

Test phase

Responses were faster when executing familiar sequences than when executing unfamiliar sequences, $F(1,14)=23.1$, $p<.001$; participants became faster during the test phase, $F(2,28)=32.5$, $p<0.001$ (see Table 3.1), and there was an effect of Key, $F(5,70)=11.8$, $\varepsilon=0.50$, $p<0.001$, see Figure 3.2 (mean RT for Key 1 to Key 6,

respectively 368.1, 284.8, 306.4, 312.9, 320.0, 224.5). The decrease in RT as a function of Block was larger for unfamiliar sequences than for familiar sequences, as was shown by a significant interaction between Familiarity and Block, $F(2,28)=8.8$, $p=0.001$. The interaction between Familiarity and Key is shown in Figure 3.2, $F(5,70)=5.4$, $p<0.001$. Post-hoc tests showed that especially key 4 and 5 were executed faster in the familiar sequence as compared to the unfamiliar sequence, respectively $F(1,11)=21.3$, $p=0.001$ and $F(1,11)=25.9$, $p=0.001$.

More correct responses were made for familiar than for unfamiliar sequences, $F(1,14)=34.3$, $p<0.001$, the number of correct responses increased during the test phase, $F(2,28)=13.5$, $p<0.001$, and there was an effect of Key, $F(5,70)=6.9$, $\varepsilon=0.39$, $p=0.002$ (mean PC for Key 1 to Key 6, respectively 94.7, 93.2, 91.5, 89.8, 88.3, 90.9). There was a larger increase in the number of correct responses for unfamiliar sequences compared to familiar sequences, as was shown by the interaction between Familiarity and Block, $F(2,28)=5.5$, $p=0.01$. Finally, on 6.4 % of the nogo trials a response was given. In sum, participants became faster and made more correct responses during the test phase, especially with unfamiliar sequences. This indicates that participants still learned the sequences during the test phase and more so the unfamiliar than the familiar sequences.
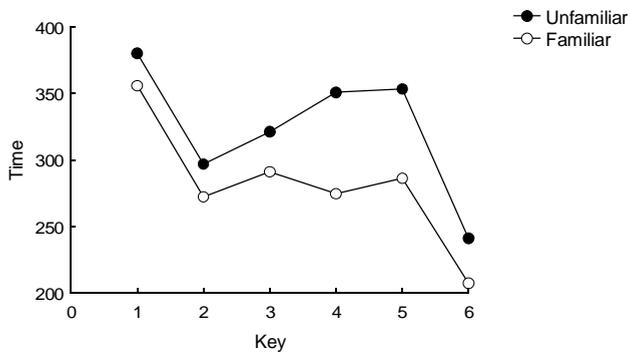
Figure 3.2 Mean response time in the test phase as a function of Key and Familiarity.

EEG analyses

CNV
The CNV at Fz, Cz, and Pz electrodes for left and right hand sequences, the topographic maps for activity averaged across the 200 ms interval before the go/nogo-signal, and source locations accounting for activity from -800 to 0 ms before the go/nogo-signal as a function of Familiarity are displayed in Figure 3.3. Figure 3.3 reveals an increased CNV for unfamiliar sequences at Cz, a comparable

CNV for familiar and unfamiliar sequences at Pz, and an increased positivity at Fz (increased for familiar sequences with left hand sequences and increased for unfamiliar sequences with right hand sequences). Inspection of the topographic maps shows a parietal negative maximum for familiar and unfamiliar sequences, preceding both left and right hand responses. In all cases, sources describing CNVs were localized near the central sulcus. Statistical analyses performed on the 1200-0 ms interval relative to the go/nogo stimulus showed a main effect of Electrode; due to positivity at Fz and negativity at Cz and Pz, $F(2,28)=36.1$, $\varepsilon=0.71$, $p<.001$. The interaction between Time and the Posterior-anterior axis, $F(10,140)=31.3$, $\varepsilon=0.25$, $p<.001$, showed that positivity at Fz and negativity at Cz and Pz increased over time, being larger on Pz than on Cz (see Figure 3.3). More importantly, a three-way interaction between Hand, Familiarity and the Posterior-anterior axis was observed, $F(2, 28)=7.0$, $p=.003$. Planned comparisons showed an increasing negativity for unfamiliar sequences compared with familiar sequences at Cz, both for left hand and for right hand trials, $F(1,14)=15.73$, $p=.001$ and $F(1,14)=12.85$, $p=.003$. Furthermore, planned comparisons showed an increasing positivity at Fz for familiar sequence compared with unfamiliar sequence for the left hand, $F(1,14)=5.59$, $p=.03$.

Source analyses were performed in order to determine the likely brain areas from which CNV activity originates. Inspection of the GFP indicated that the time window from -800 to 0 ms before the go/nogo-signal was most appropriate for our fitting procedure. PCA showed that one component accounted for at least 97.1 % of the variance in all four conditions (left hand familiar sequence, left hand unfamiliar sequence, right hand familiar sequence, right hand unfamiliar sequence). Since left and right handed responses were given and there are probably interhemispheric connections, bilateral activity was expected to be observed. Therefore, one symmetrical source pair was fitted for each condition. After the fitting procedure, the RV amounted to 14.8% for the left hand familiar sequence condition, 14.4% for the left hand unfamiliar sequence condition, 9.2% right hand familiar sequence condition and 10.4% for the right hand unfamiliar sequence condition. Although spatial resolution of the source localization is limited, in all four conditions the symmetrical source pair appeared to be localized around the central sulcus, which probably reflects activity from M1, the premotor cortex and/or SMA (see Figure 3.3). In summary, an increasing central CNV was shown for unfamiliar sequences compared to familiar sequences, originating from motor areas. This suggests and that there is a quantitative rather than a qualitative difference in general motor preparation between familiar and unfamiliar sequences with the left and right hand.
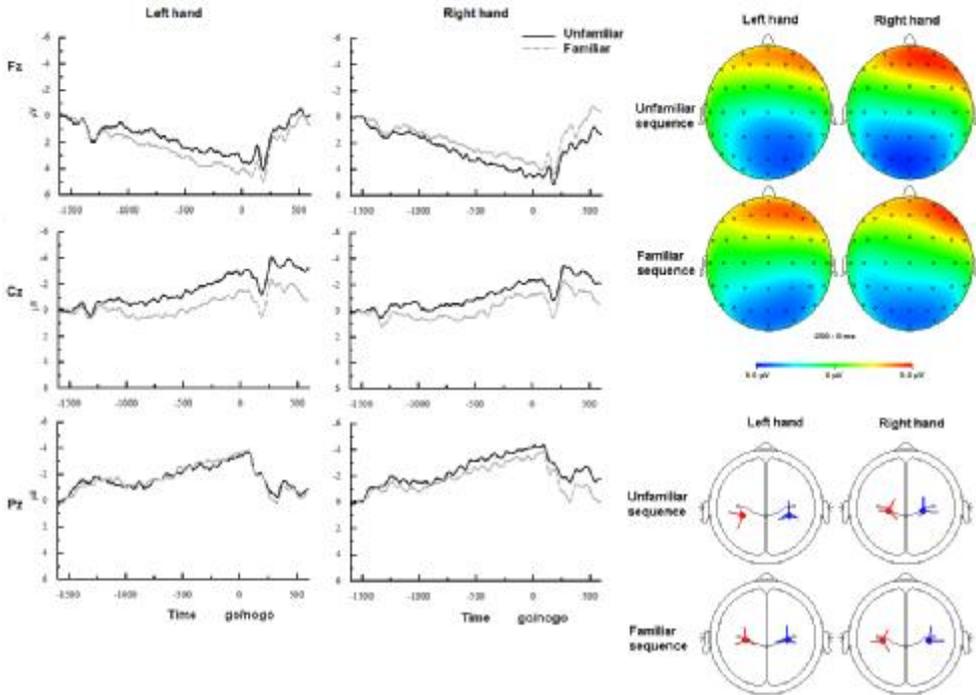
Figure 3.3 Left: event-related brain potentials at Fz, Cz and Pz as a function of Familiarity and Hand. Right top: topographic maps of the 200 ms interval before the go/nogo-signal as a function of Familiarity and Hand. Right bottom: estimated source model for preparation-related activity for the 800-0 ms interval before the go/nogo-signal as function of Familiarity and Hand.

LRP

The LRP as function of Familiarity, topographic maps for averaged activity within the 200 ms interval before the go/nogo-signal as function of Familiarity and source locations accounting for the LRP related activity are displayed in Figure 3.4. Figure 3.4 reveals an increasing negativity during the preparation of familiar and unfamiliar sequences. The data in the topographic maps were arranged such that the right electrodes in Figure 3.4 represent the lateralized ERP activity and the left electrodes represent the mirror version of the right electrodes. Inspection of the topographic maps shows lateral activation at central sites for unfamiliar and familiar sequences, which may reflect motor related activity for unfamiliar and familiar sequences. Source locations accounting for the peak of the LRP shows a central lateral source, probably located in the M1 and/or premotor cortex. The peak of the LRP was largest at C3/4, therefore LRP analyses were performed on C4. Statistical analyses performed on the 1200 ms prior to the go/nogo interval revealed that the

LRP increased over time (mean amplitude in µV for the 200ms time intervals from -1200 to 0 ms before the go/nogo, respectively; -.052, -0.88, -0.89, -0.99, -1.21 and -1.24), $F(5,70)=7.1$, $\varepsilon=0.33$, $p=0.006$. Furthermore, results showed that overall the LRP deviated from zero, $F(1,14)=11.5$, $p=.004$, but there was no difference in LRP amplitude between familiar and unfamiliar sequences, $F(1,14)=0.2$, $p=.7$[1].
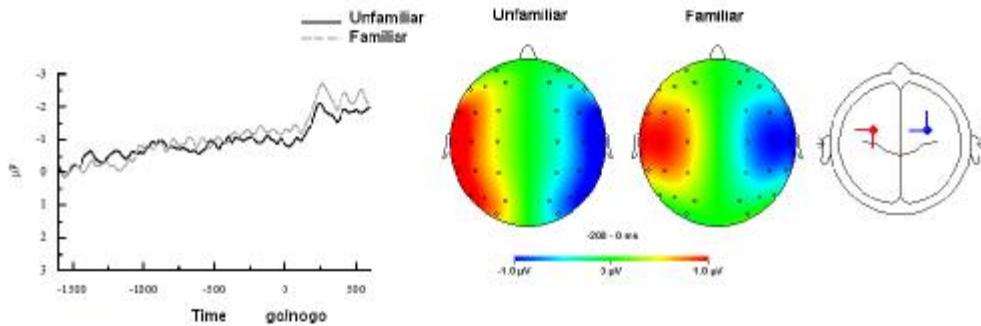

Figure 3.4 Left: stimulus-locked lateralized readiness potential (LRP) as a function of Familiarity for the central (C3/4) electrode pair. Middle: topographic maps of lateralized activity of the 200 ms interval before the go/nogo-signal. The data was arranged such that the right electrodes in Figure 3.4 represent the lateralized ERP activity and the left electrodes represent the mirror version of the right electrodes. Right: source model accounting for the peak of the LRP.

Source analyses were performed in order to determine the likely brain areas from which LRP activity originates. As no reliable difference in LRP amplitude was found between familiar and unfamiliar sequences, averaged activity of familiar and unfamiliar sequences was used for our fitting procedure. The peak of the LRP was used for our fitting procedure to maximize the signal to noise ratio, which was located at 250ms after the go/nogo-signal. A PCA showed that one component accounted for 89.6 % of the variance. Since the left electrodes represent the mirror version of the right electrodes, one symmetrical source pair was fitted. After the fitting procedure, the RV amounted to 12.4%. Figure 3.4

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[1] Additional analyses were performed on the LRP, in which we included activity at the PO7/8 electrodes as a covariate. An interaction between Familiarity and Time–interval might reflect a difference in LRP amplitude between familiar and unfamiliar sequences, $F(5,69)=2.60$, $\varepsilon=0.43$, $p=.033$. Thus, when controlling for lateralized activity at PO7/8 an increasing difference in LRP amplitude between familiar and unfamiliar sequences was shown. However, this difference was small, and its locus (see CDA analyses) appears to be posterior, which makes an interpretation in terms of a difference in motor activity unlikely.

displays the obtained source locations, which seems to reflect activity from M1 and/or the premotor cortex. In summary, an LRP was found for familiar and unfamiliar sequences, originating from motor areas, however, no reliable difference in LRP amplitude was found between familiar and unfamiliar sequences.

CDA

The CDA as function of familiarity, the topographic maps for averaged activity within the 500 ms interval before the go/nogo-signal as a function of Familiarity and source locations accounting for the difference in activity between unfamiliar and familiar sequences are displayed in Figure 3.5. Figure 3.5 reveals an increasing negativity when preparing unfamiliar sequences as compared to familiar sequences. The topographic maps, showing the time-interval at which the difference between familiar and unfamiliar sequences was maximal, indicate lateral activation at posterior sites for the unfamiliar sequence, but not for familiar sequences. This may reflect memory related activity for unfamiliar sequences but not for familiar sequences. Source location of the difference between familiar and unfamiliar sequences shows a lateral posterior source, which indeed can be related to increased activity of visual working memory in case of unfamiliar sequences. Statistical analyses performed on the 1200 ms prior to the go/nogo interval showed a main effect of Time-interval (mean amplitude for the 200ms time intervals from -1200 to 0 ms before the go/nogo stimulus, respectively; -0.42, -0.88, -0.86, -0.69, -0.60 and -0.45 μV), $F(5,70)=3.5$, $ε=0.44$, $p=0.039$. The main effect of Familiarity showed that the amplitude of the CDA was larger for unfamiliar sequences than for familiar sequences (mean amplitude for familiar and unfamiliar sequences, respectively; -0.34 μV and -0.96 μV), $F(1,14)=4.6$, $p=.05$. Furthermore, results showed that overall the CDA deviated from zero, $F(1,14)=9.8$, $p=.007$. Extra analyses in which we included activity at C3/4 as a covariate showed that the CDA remained larger for unfamiliar sequences as compared to familiar sequences, $F(1,13)=4.94$, $p=.045$.

        Source analyses were performed in order to determine the likely brain areas from which the difference between familiar and unfamiliar sequences originates. For our fitting procedure the activity of familiar sequences was subtracted from activity of unfamiliar sequences. Inspection of the GFP indicated that the time window from -800 to 0 ms before the go/nogo-signal was most appropriate for our fitting procedure. PCA showed that one component accounted for 95.2 % of the variance. Again, one symmetrical source pair was fitted. After the fitting procedure, the RV amounted to 48.5%. Figure 3.5 displays obtained source locations for the difference in activity between familiar and unfamiliar sequences, which reflects activity from posterior brain areas. In summary, the difference in lateralized activity between familiar and unfamiliar sequences probably originates

from posterior areas, probably reflecting an increased load on visual-working memory in case of unfamiliar sequences.
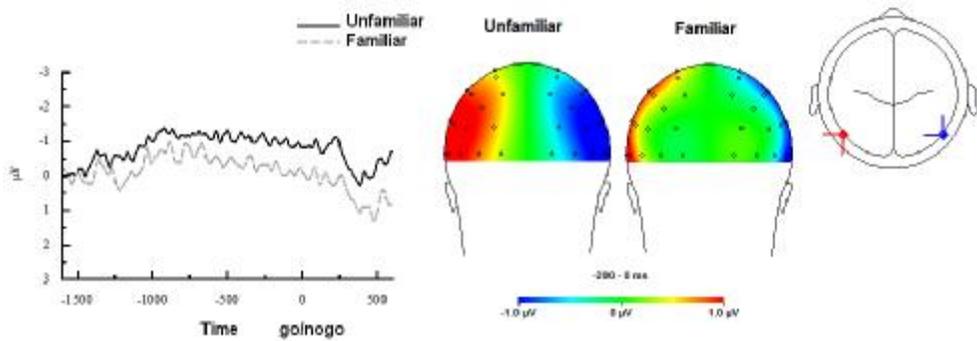

Figure 3.5 Left: stimulus-locked contralateral delay activity (CDA) as a function of Familiarity for the occipito-parietal (PO7/8) electrode pair. Middle: topographic maps of the lateralized activity of the 200 ms before the go/nogo-signal. The data was arranged such that the right electrodes in Figure 3.5 represent the lateralized ERP activity and the left electrodes represent the mirror version of the right electrodes. Right: source model for the difference in activity between unfamiliar and familiar for the 200-0 ms interval before the go/nogo-signal.

3.4 Discussion

The goal of the present study was to investigate if practice of discrete sequences corresponds with a shift from general motor preparation to effector specific motor preparation, as may be predicted on the basis of the model by Hikosaka et al. (1999), or with a decreasing demand on general motor preparation and an equal load on effector specific motor preparation, as may be predicted on the basis of the model by Verwey (2001). Furthermore, it was investigated if sequence learning develops from an attentive to an automatic phase (e.g., Cohen et al., 1990; Doyon & Benali, 2005; Verwey, 2001). Participants performed a go/nogo DSP task in which, in case of a go-signal, familiar and unfamiliar sequences were to be executed. We used the late CNV, LRP and CDA to index general motor preparation, effector specific motor preparation and visual-working memory, respectively.

Results showed an increased CNV and CDA for unfamiliar sequences as compared to familiar sequences and a comparable LRP for familiar and unfamiliar sequences. Furthermore, source localization on the CDA showed that the difference of lateralized activity between the preparation of familiar and unfamiliar sequences originated from posterior sites, whereas LRP and CNV related activity

both originated from motor areas. This implies that the difference between the preparation of familiar and unfamiliar sequence concerns the involvement of general motor preparation and the load on visual-working memory, being enlarged for unfamiliar sequences. General motor preparation is thought to reflect the presetting of responses, as will be discussed in more detail later. We suggest that with unfamiliar sequences each individual stimulus may have to be kept in visual-working memory and each individual response may have to be preset, whereas with familiar sequences segments of stimuli (chunks) can be stored in visual-working memory and segments of responses (chunks) can be preset. This implies a reduced demand on visual working memory and the presetting of responses for familiar sequences. Furthermore, since the CNV originated from motor areas, a close link between the presetting of responses and effector specific motor preparation is suggested.

Our results are in line with and extend the model of Verwey (2001) in that with practice chunks can be presetted instead of individual responses, which seems to imply a differential demand on visual working memory, while effector specific motor preparation appears to be comparable for familiar and unfamiliar sequences. We suggest that with practice the load on the presetting of the responses (cognitive component) decreases, as chunks are presetted instead of individual responses, and effector specific preparation (motor component) remains the same, as chunks or separate elements are loaded into the motor buffer, which is independent of learning. Since we presented the stimuli in a visual-spatial format and the demand on visual-working memory decreased with practice it seems likely that the responses are presetted in a visual-spatial format. In the present study the practiced sequences are always executed with the practiced hand, therefore it is unclear if this presetting is effector specific or not. In addition, as we used visual-spatial stimuli which probably resulted in presetting responses in a visual-spatial format, it would be interesting to investigate the influence of stimulus-modality on the format in which the responses are presetted.

In the following we will more closely focus on the interpretation of our physiological measures, first regarding our lateralized components (CDA and LRP). When controlling for CDA activity an increasing difference in LRP amplitude during the length of the preparation interval between unfamiliar and familiar sequences was found. However, as this effect was small and only present when controlling for CDA activity, it seems trivial. In addition, source localization showed that the difference between familiar and unfamiliar sequences originated from posterior sites. Therefore we suggest that the difference between familiar and unfamiliar sequences was caused by the reliance on visual-working memory and not by the reliance on effector specific motor preparation. Thus, given that the amplitude of the CDA reflects the amount of information held in visual-working memory (Vogel &

Machizawa, 2004) we suggest an increased visual-working memory load for unfamiliar sequences. Moreover, since the difference between familiar and unfamiliar sequences originated from posterior sites, we suggest that the CDA has a posterior source, probably originating from the visual cortex.

Regarding the interpretation of our motor components (CNV and LRP), source localization showed that both CNV and LRP related activity may originate from (pre)motor areas. Since the CNV was increased for unfamiliar sequences and the LRP was identical for familiar and unfamiliar sequences, we suggest that both originate from different sources. Previous studies suggested that CNV activity originates in M1 and/or SMA (Cui, et al, 2000; Leuthold, Sommer, & Ulrich, 2004) and LRP activity originates in M1 (e.g. Leuthold & Jenzsch, 2002a, Jentzsch et al., 2004; Leuthold et al., 2004) and/or premotor cortex (Shibasaki & Hallett, 2006). As these areas are located close to each other, source localization may be unable to distinguish between these sources, as was already predicted by Praamstra, Stegeman, Horstink, & Cools (1996). However, source localization on the CNV at least clarified that this negativity most likely originates from (pre)motor areas and not from frontal or posterior areas.

This observation may be related to the interpretation of the CNV as given in our introduction. According to Verleger et al. (2000b) the late CNV represents the presetting of possible responses. In their task precues were provided with full, partial or no information about the movement which could be valid or invalid. In case of partial or no information, this resulted in the parallel preparation of several responses. In the present study precues always indicated the correct response, which suggests that parallel preparation of several responses cannot account for the late CNV in the present study. Nevertheless, as a sequence of responses had to be executed instead of a single response, it could be argued that the presetting of several responses is reflected in the CNV. In line with this, Cui et al. (2000) suggested that the late CNV reflects the level of preprogramming, as an increased CNV was found for complex movements as compared to simple movements. In the present study this level of preprogramming could imply the presetting of the sequence of responses. Thus, in correspondence with Verleger et al. (2000b) and Cui et al. (2000) we interpret the CNV effect as a reflection of the difference in preparation of unfamiliar (complex) and familiar (simple) responses, in that with unfamiliar sequences each individual response had to be presetted, whereas with familiar sequences segments of responses (chunks) were presetted, which is less demanding.

Alternative interpretations of the CNV are given by Brunia & Van Boxtel (2001) and Ruchkin et al. (1996), who suggest that non-motoric processes such as stimulus anticipation and visuospatial working memory also contribute to the late CNV. In the present study, however, anticipation for the go/nogo stimulus is

identical for familiar and unfamiliar sequences, suggesting at least that differences between these sequences are not reflected in the late CNV. With regard to the involvement of visual-working memory, this could indeed be reflected in the late CNV in the present study, as a sequence of visually stimuli had to be remembered. Nevertheless, our source analyses point to a source in primary and/or premotor cortex, which makes an interpretation of our CNV effects in terms of a differential load on visual-working memory unlikely.

Source localization showed that presetting of responses occurs in (pre)motor areas, as activity within symmetrical lateral sources was sufficient to describe activity preceding the go/nogo-signal. Nevertheless, Leuthold and Jentzsch (2001) found a three-dipole solution during movement preparation, with sources in lateral and medial sites. The medial source was thought to originate from the SMA and reflecting the selection of abstract motor preparation, whereas the lateral dipoles were thought to originate from M1 and reflecting effector-specific motor preparation. An important difference between the present study and the study of Leuthold and Jentzsch (2001) is that they provided precues with full, partial or no information about the movement that could be valid or invalid, whereas we always provided complete information about the upcoming movement. This difference probably resulted in the absence of a medial source in the present study.

Concluding, we suggest that with familiar sequences chunks of stimuli are kept in visual-working memory and chunks of responses are presetted at a motor level, whereas with unfamiliar sequences individual stimuli are memorized and presetted. Future research should clarify if this presetting is effector specific or not and if it is influenced by stimulus-modality.

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4 Preparing mirrored motor sequences[*]

Abstract

The same writing style is demonstrated with the dominant and the non-dominant hand of a person. Specifically, the shapes produced by the dominant and non-dominant hand of the same person are similar in several respects. This and other findings have been ascribed to a common representation of the movements required. In the present study, the question was raised whether this representation is indeed in a general motor format or in a more abstract non-motor format. If the contingent negative variation (CNV), which is thought to reflect general motor preparation, is identical for familiar and mirrored sequences, this would support the interpretation of a general motor representation. Fixed series of five keypresses, which could be familiar, unfamiliar or mirrored, had to be prepared and executed/withheld after a go/nogo-signal. Results showed an increased demand on generalized motor preparation before unfamiliar sequences, compared with both familiar and mirrored sequences. Source localization showed that the CNV originated from motor areas and frontal areas. Together, our findings support the idea that preparation of sequences involves the presetting of an effector-independent representation in a general motor format that can be employed by different effectors.

4.1 Introduction

We are able to write down our name with our non-dominant hand or even with a pencil in our mouth. Most striking about this writing is that the style of writing is rather similar across motor systems of the same person (Keele, 1981). These observations have been considered as support for the concept of a generalized motor program (GMP) (Schmidt, 1975; Keele et al., 1995). A GMP is an effector-independent representation that can be used to execute a movement. However, it remains unclear if this effector-independent representation is indeed in a general motor format or in a more abstract non-motor format, for example, in a spatial format.

A way to differentiate between these two options is to study mirrored movement sequences, which are sequences of which the stimuli are mirrored around a central point. A task suitable for studying mirrored movement sequences is the discrete sequence production (DSP) task. In a typical DSP task, several discrete sequences are practiced extensively by responding to fixed series of three

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[*] In preparation−b, De Kleine, E., & Van der Lubbe, R.H.J.

to seven key-specific visual stimuli. All but the first stimulus are presented immediately after the response to the previous stimulus, and there typically are a limited number of sequences. In the DSP task the execution of mirrored versions of practiced sequences (from now on called mirrored sequences) with the unpracticed hand leads to the movement of the homologue fingers of the unpracticed hand. However, the execution of mirrored sequences with practiced hand leads to the movement of different fingers of the practiced hand. Therefore different representations are used during the execution of mirrored sequences with the practiced and the unpracticed hand; a mirrored sequence executed with the unpracticed hand can use a general motor representation of the movement in which the fingers are specified, but not the hand, whereas the mirrored sequence executed with the practiced hand can not use such a representation. Thus, if the effector-independent representation is in a general motor format, it is expected that the CNV, which is considered to reflect general motor preparation (Leuthold & Jentzsch, 2001), is identical for familiar sequence executed with the practiced hand and mirrored sequences executed with the unpracticed hand. However, when the effector-independent representation is in an abstract (for example spatial) format, it has to be transformed before it can be used for mirrored sequences executed with the unpracticed hand. In this case, it is expected that the CNV is identical for mirrored and unfamiliar sequences, since the mirrored sequence is new, on a motor level, and therefore there is no advantage on a motor level.

Previous studies observed transfer from practiced to mirrored movement sequences in the serial reaction time (SRT) task (Wachs, Pascual-Leone, Grafman, & Hallett, 1994; Grafton, Hazeltine, & Ivry, 2002; Verwey & Clegg, 2005). In the SRT task stimulus presentation and response execution are identical to the DSP task, but in the SRT task participants continuously cycle through a fixed series of 8-12 keypresses, and there usually is an interval of about 200 ms between a response and the next stimulus. Since participants are quite often unaware of the repeating movement sequence, the SRT task is suitable for studying explicit and implicit motoric sequence learning. Grafton et al. (2002) proposed two possible explanations for the benefit of mirrored sequences executed with the unpracticed hand in the SRT task; the effector-independent representation could be used for mirrored sequences, or the effector-dependent representation could be transformed to the other effector. Results of their study demonstrated transfer to mirrored sequences executed with the unpracticed hand, but sequence execution with the unpracticed hand was faster for the practiced sequence, as compared with mirrored sequences. Since mirrored sequences were executed slower than the original sequences with the unpracticed hand, Grafton et al. (2002) suggested that the execution of mirrored sequences with the unpracticed hand involves the same

effector-dependent representation as the original sequence, but that additional processes are recruited to perform the transformation.

Another explanation for the benefit of mirrored sequences executed with the unpracticed hand in the SRT task was proposed by Verwey and Clegg (2005). They suggested that a motor representation may develop that controls the order of particular fingers (hand postures), irrespective of the hand. Results showed transfer to mirrored sequences, but the execution of mirrored sequence was equally fast with the practiced and the unpracticed hand. This finding suggests that hand posture learning is not responsible for the execution of mirrored sequences with the unpracticed hand. In line with Grafton et al. (2002), Verwey and Clegg (2005) suggested that the execution of mirrored sequences with the unpracticed hand includes the same representation as the original sequence, and that additional processes are recruited to perform the transformation. However, it remains unclear if this effector-independent representation is in a motor format or a more abstract spatial format.

No previous studies examined transfer to mirrored sequences in the DSP task. The DSP-task seems very suitable to study transfer, since segmentation can be studied with the DSP-task, and the transfer of segmentation patterns may inform us about underlying representations. In the present study we focused on the preparation of movement sequences and their execution. According to several authors, the same processes are involved in sequence preparation and sequence execution (Catalan, Honda, Weeks, Cohen, & Hallett, 1998; Jeannerod, 1994). However, studying sequence preparation can give a better view on the precise function of the processes underlying sequences as compared with motor execution, since measures of execution of a sequence are contaminated with the preparation of forthcoming responses. Given that preparation is covert, measures derived from the EEG appear especially useful to study movement preparation (e.g. Dirnberger et al., 2000; Van der Lubbe, et al., 2000). The CNV can possibly be used to differentiate between an explanation in terms of general motor representation or in terms of an abstract representation. The CNV is a negative going wave with mostly a central maximum that unfolds in the interval between a warning stimulus and an execution signal (e.g. a go/nogo-signal) (Jentzsch & Leuthold, 2002; Verleger, Vollmer, Wauschkuhn, Van der Lubbe, & Wascher, 2000), which is considered to reflect general motor preparation (Leuthold & Jentzsch, 2001).

In a previous study (De Kleine & Van der Lubbe, in preparation-a), we examined the preparation phase of familiar and unfamiliar sequences. Participants performed a go/nogo DSP task in which six key-specific stimuli were subsequently presented, which after a preparatory interval were followed by a go/nogo-signal. In case of a go-signal, participants were to react as fast and accurately as possible by

pressing the six corresponding keys in the indicated order, and in case of a nogo-signal responses should be withheld. This modified DSP task allowed us to study the preparation phase of sequence learning in isolation from motor execution. Results showed that the CNV was increased before unfamiliar sequences, as compared with familiar sequences. This implies that generalized motor preparation was increased for unfamiliar sequences, as compared with familiar sequences. Furthermore, source localization results showed that general motor preparation originated from primary and/or premotor cortex, suggesting that the CNV is indeed related to motor preparation and not to abstract preparation. If the CNV is related to abstract preparation, for example in spatial coordinates, then a parietal source would be expected.

In the present study, we questioned if an effector-independent representation (a GMP) reflects a general motor representation or an abstract representation of a sequence. In the present experiment familiar, unfamiliar and mirrored sequences were prepared and executed using the go/nogo DSP task. Mirrored sequences were executed with the unpracticed hand and behavioral and EEG measures were used to examine the preparation and execution of sequences. In agreement with Grafton et al. (2002) and Verwey and Clegg (2005) we suggested that the execution of mirrored sequences would be slower than familiar sequences and faster than unfamiliar sequences. It was predicted that if the effector-independent representation was in a general motor format, it could be used for practiced sequences executed with the practiced hand and for mirrored sequences executed with the unpracticed hand, as the homologue fingers of the unpracticed hand are used. This would suggest an identical CNV for familiar and mirrored sequences. In contrast an identical CNV for unfamiliar and mirrored sequences suggests that the effector-independent representation reflects abstract preparation, for example is spatial coordinates. Finally, if the segmentation pattern transfers from the practiced sequence to the mirrored sequence executed with the unpracticed hand, it shows that segmentation is not effector specific, but possibly general motoric or abstract format.

An additional goal of the present study was to replicate the CNV results of our previous study, in which we observed that general motor preparation, indexed by the CNV, was increased before unfamiliar sequences compared with familiar sequences (De Kleine & Van der Lubbe, in preparation-a). In contrast to our previous study, we decided to set the baseline for our EEG analyses at the 100 ms interval before the presentation of the first stimulus and not at the 100 ms interval before the start of the go/nogo-signal, during which the last stimulus was still present. It could be that with familiar sequences participants paid less attention to stimuli, since they already know after a few stimuli which sequence is presented (as it is familiar). In contrast, with unfamiliar sequences participants have to pay

attention to the last stimulus, as the sequence is unknown to them. In principle, this could result in a different EEG pattern in the 100 ms interval before the go/nogo-signal. Therefore, in the present study we set the baseline at the 100 ms interval before the presentation of the first stimulus. Another difference with our previous study is that we used 5 key sequences in the present study instead of 6 key sequences. Since an additional condition with mirrored sequences was included in the present study, the number of sequences to be prepared and executed was larger. In order to keep the duration of the experiment acceptable we used 5 key sequences instead of 6 key sequences.

4.2 Methods

Participants
Eighteen students (4 males, 14 females), aged 19-26 years (mean: 22 years) from the University of Twente served as participants. Participants had a mean handedness score of 19 (range: 12-24), measured by the Annett Handedness Inventory (Annett, 1970), signifying that all participants can be considered as right-handed. All participants gave their written informed consent and reported normal or corrected-to-normal vision. Participants received course credits for their participation of maximally 7 hours divided across two days. The study was approved by the local ethics committee of the Faculty of Behavioral Sciences of the University of Twente and was performed in line with the Declaration of Helsinki.

Stimuli
Participant placed their little finger, ring finger, middle finger and index finger of their left and right hand respectively on the a, s, d, f keys and the ;, l, k, j keys. A trial consisted of the presentation of five stimuli. They were followed by a go or a nogo stimulus, which indicated if a sequence was to be executed or not. In case of a subsequent go stimulus, a trial was to be followed by the execution of the five spatially corresponding keypresses (one sequence). The presentation of the stimuli is displayed in Figure 4.1. Each trial started with the presentation of a fixation-plus (1.3°) in the center of the screen and eight horizontally aligned squares (2.5°), four on the left and four on the right side of the fixation-plus. The alignment of the eight stimulus squares corresponded with the alignment of the eight response keys and had a total visual angle of 26.5°. The eight squares and the fixation-plus were drawn with a silver color line on a black background. After 1000 ms one of the squares was filled yellow for 750 ms, next, a second square filled yellow for 750 ms, etc., until a fifth square. Next, the default screen was presented for 1500 ms. After this interval, the fixation-plus was colored either red (6%) or blue (94%). A red

fixation-plus stayed on the screen for 3000 ms and indicated that no action should be executed (a nogo trial). A blue fixation-plus (for 100 ms) indicated that participants had to press the buttons corresponding to the presented sequence of yellow squares (a go trial). Participants were instructed to respond as fast and accurate as possible, and were requested to keep their eyes on the fixation-plus during the preparation interval. Feedback on the correctness/incorrectness of the responses was given after producing the response sequence. In case of a response before the go/no-go-signal, the words "te vroeg" were presented (Dutch equivalent of too soon).
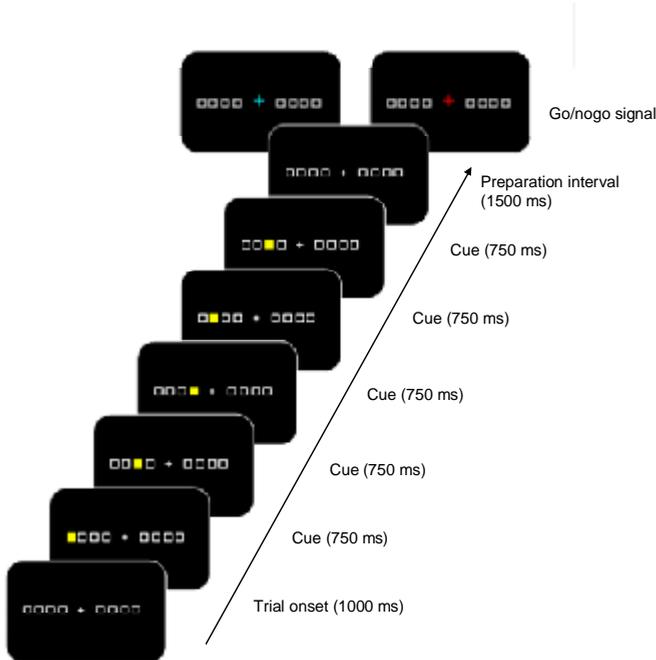
Figure 4.1 An example of the sequence of stimuli from the start of a trial until the go/nogo-signal. The duration of each stimulus frame is indicated along the time axis.

In the present experiment, participants practiced eight familiar sequences during the learning phase, which were randomly presented. Every participant received four sequences for the left hand, and four sequences for the right hand. In order to counterbalance across participants and across fingers eight different structures of sequences were used; 12432, 23143, 34214, 41321, 13243, 24314, 31421, 42132. With each structure four sequences were created by the assignment of different keys to the numbers, to eliminate finger-specific effects. The first structure leads to the sequences asfds, sdafd, dfsaf and fadsa, and so on for the

seven other structures. The four sequences of each hand started with a different key press and at the same time the four sequences had a different structure. This led to four different versions of sequences, which were counterbalanced across participants. During the test phase, four practiced sequences, four mirror versions of the practiced sequences (aà;, sàl, dàk, fàj) and four new sequences were randomly presented to the participants. Half of the sequences were carried out with the left hand and the other half with the right hand, equally divided within blocks. The versions were counterbalanced across the test phase and practice phase, in that the unfamiliar sequences of one group were the familiar sequences of a second group. Thus, differences observed between familiar and unfamiliar sequence could not be due to the specific sequence employed, or to finger specific effects.

Procedure

Participants were tested on two days. On the first day, they had to perform five practice blocks, each consisting of 96 sequences (12 repetitions of each sequence and eight no-go trials). On the second day, they were presented with one practice block (which led to 72 repetitions of each practiced sequence) and three test blocks, each consisting of 120 sequences (ten repetitions of each sequence and eight no-go trials). During the test phase, EEG was recorded, which led to a pause of approximately 90 minutes between the last practice block and the first test block, as the EEG equipment had to be implemented. Halfway each block, a pause of 20 sec was provided in which the participant could relax. During this break and at the end of each block, the participants received feedback about their performance (mean RT and amount of errors). Every block was followed by a small break of approximately 2 minutes, and every other block was followed by a break of approximately 10 minutes.

Recording and data processing

The experiment was run on a personal computer (Pentium 4) with a QWERTY keyboard. Stimulus presentation, response registration, and production of external triggers were controlled by E-Prime, version 1.1. A 17 inch monitor was placed in front of the participants at a distance of about 60 cm. EEG, electro-oculogram (EOG), and electro-myography (EMG) was amplified with a Quick-Amp amplifier (72 channels DC) and recorded with Brain Vision Recorder (version 1.05) software. EEG was recorded from 61 Ag/AgCl ring electrodes located at standard electrode positions of the extended 10/20 system. An online average reference was employed. EOG was recorded bipolarly, both vertically from above and below the left eye, and horizontally from the outer canthi of both eyes. EMG from left and right forearm (musculus flexor digitorum superficialis) was recorded. Electrode

impedance was kept below 5 kΩ. The EEG, EOG, and EMG data were sampled at a rate of 500 Hz. Measured activity was digitally filtered online (low-pass 140Hz, DC).

Data analysis

For statistical analyses, the Greenhouse-Geisser epsilon correction was applied whenever appropriate. Furthermore, EEG analyses were performed on all data without artifacts. We did not eliminate trials with an incorrect response as it would unnecessarily reduce the total amount of trials, and might additionally introduce a bias for familiar vs. mirrored vs. unfamiliar sequences due to an unequal number of trials in each condition. The interval between the offset of the last stimulus and the go/nogo-signal was 1500 ms. The data was segmented starting 5350 ms before the go/nogo-signal until 600 ms after the go/nogo-signal. A baseline was set at the 100-0 ms interval before the presentation of the first stimulus, during which the fixation-plus and the eight horizontally aligned squares were presented. Trials with EMG artifacts and/or out of range values in the 1200 ms before the go/nogo-signal were excluded from further analyses. We corrected for EOG artifacts by using the Adaptive Model approach of Brain Electrical Source Analysis (BESA) (version 5.1.6). Finally, a low-pass filter with a cut-off at 16 Hz was applied to event-related brain potentials of individual participants to calculate the CNV.

Response parameters

Response time (RT) was defined as the time between onset of the go-signal and depression of the first key, and as the time between the onsets of two consecutive keypresses within a sequence. The first two trials of every block and after every break and trials with errors were excluded from RT analyses. Trials in which the total RT, the sum of 5 RTs, deviated more than 3 SD from the overall mean total RT per block across participants were additionally eliminated from the RT analysis. This procedure removed 0.9% of the trials. The Percentage Correct (PC) was calculated as the percentage correct key-presses. The mean RTs and mean PC were evaluated statistically by analysis of variance (ANOVA) with repeated-measures, with in the practice phase Block (6), Key (5) and Hand (2) as within subject factors and in the test phase Block (3), Key (5), Hand (2) and Condition (familiar, mirrored or unfamiliar sequence) as within-subjects factors.

EEG parameters

Statistical analyses were performed on the interval from -1200-0 ms before the go/nogo-signal. The CNV was statistically analyzed for the Cz and the Fz electrode by averaging EEGs for all trials without artifacts. Cz was used since the predominant distribution of the CNV in our previous study was on Cz (De Kleine &

Van der Lubbe, in preparation-a) and Fz was used since source analysis showed a frontal source in addition to a central source. Analyses included the factors Time Interval (6), Condition (familiar, mirrored or unfamiliar) and Hand (2). One-sided tests were used for the interaction between Time and Condition, since we had specific predictions, based on our previous study (De Kleine & Van der Lubbe, in preparation-a).

Source analyses were performed on averages per condition, in order to specify the brain regions accounting for CNV activity. BESA (version 5.2) was employed to determine regional sources, which can be regarded as a source with three single dipoles at the same location but with orthogonal orientations. BESA determines the location and orientation of regional sources by calculating the scalp distribution for a given model and comparing it with the original distribution. The model is optimized by minimizing the residual variance (RV) between the model and the original distribution. Determination of the time windows for the fitting procedure (see Results) was based on our previous study (De Kleine & Van der Lubbe, in preparation-a) and on the inspection of the global field power (GFP) of the grand average event related potentials. Furthermore, determination of the number of sources was based on inspection of the principal component analyses (PCA) and the source waveforms.

4.3 Results

Behavioral measures

Practice phase
RTs and PCs as a function of Hand and Condition are compiled in Table 4.1. Participants became faster with practice, $F(5,55)=35.6$, $p<0.001$, $\varepsilon=0.40$, and there was an effect of Key, $F(4,44)=9.8$, $p<0.001$ (mean RT for Key 1 to Key 5, respectively 375.2, 312.1, 344.3, 313.7 and 270.0). Furthermore, the difference in RT between keys decreased with practice, as was shown by the significant interaction between Block and Key, $F(20,220)=2.6$, $p<0.001$. Finally, there was an interaction between Hand and Key, $F(4,44)=10.8$, $p<.001$, which showed that the relapse is more pronounced for the left hand than for the right hand (see Figure 4.2).

	Hand	Sequence	Practice phase	Test phase		
				Block 1	Block 2	Block 3
RT	Left	Familiar	323	310	293	280
		Mirrored		342	314	291
		Unfamiliar		361	326	312
	Right	Familiar	323	314	286	272
		Mirrored		328	299	279
		Unfamiliar		348	308	295
PC	Left	Familiar	82.5	89.0	89.8	89.8
		Mirrored		84.8	88.4	92.3
		Unfamiliar		76.5	82.2	82.8
	Right	Familiar	81.8	90.3	93.0	90.8
		Mirrored		84.5	89.8	89.1
		Unfamiliar		80.9	85.5	90.3

Table 4.1 Mean RTs (in ms) and PC (in %) as a function of Hand and Sequence for the practice and the test phase.
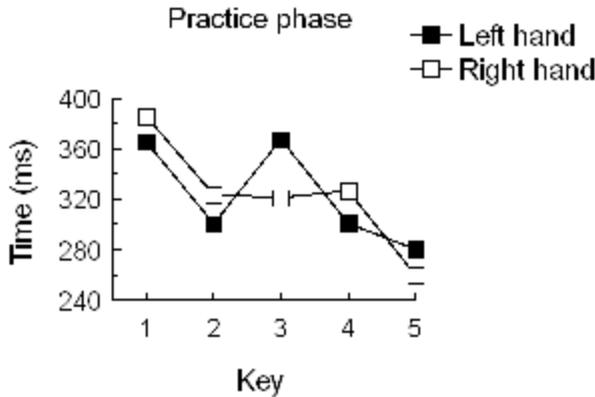

Figure 4.2 Mean response time in the practice and test phase as a function of Key and Hand.

The number of errors reduced with practice, $F(5,70)=21.4$, $p<0.001$, $\varepsilon=0.31$, and there was an effect of Key on PC, $F(4,56)=17.9$, $p<0.001$, $\varepsilon=0.47$ (mean PC for Key 1 to Key 6, respectively 90.2, 85.3, 81.4, 75.2 and 78.9). Furthermore, with practice the differences between the amount of errors between the keys decreased, as was shown by the significant interaction between Block and Key, $F(20,280)=4.0$, $p<0.001$. Summarizing, due to practice participants became

faster, made less errors, and the differences between the keys within the sequence in RT and PC decreased, signifying that participants learned the sequences. Finally, the relapse in RT, due to segmentation, was more pronounced for the left hand than for the right hand.

Test phase

RTs and PC as a function of Block, Hand and Condition are compiled in Table 4.1. There was a main effect of Condition, $F(2,34)=12.0$, $p<.001$ (mean RT for familiar 293 ms, for mirrored 309 ms, for unfamiliar 325 ms). Planned comparisons showed that responses for familiar sequences were faster than for mirrored sequences ($F(1,17)=4.6$, $p=.05$), and responses to mirrored sequences were faster than for unfamiliar sequences ($F(1,17)=10.5$, $p=.005$). Furthermore, participants became faster during the test phase, $F(2,34)=38.7$, $p<0.001$, $\varepsilon=0.63$ (mean RT for block 1 334 ms, for block 2 305 ms and for block 3 288 ms), and there was an effect of Key, $F(4,68)=7.8$, $p<0.001$, $\varepsilon=0.54$ (mean RT for Key 1 to Key 5, respectively 336.9, 297.0, 335.5, 314.5 and 260.4). The interaction between Condition and Block showed that with practice in the test phase the differences between the conditions decreased ($F(4,68)=3.1$, $p=.021$), the interaction between Block and Key showed that with practice the differences between the keys decreased ($F(8,136)=3.6$, $p=.014$, $\varepsilon=0.43$) and the interaction between Hand and Key showed that the relapse in RT is more pronounced in the left hand than in the right hand ($F(4,68)=3.0$, $p<.001$) (see Figure 4.2). A planned comparison showed that the decrease in RT from Key 2 to Key 3 was larger for the left hand than for the right hand, $F(1,17)=13.2$, $p=.002$. Finally, there was a was a three-way interaction between Condition, Hand and Key, $F(8,136)=11.3$, $p<.001$, $\varepsilon=0.60$ (see Figure 4.3). This interaction shows that the segmentation pattern of the practice phase transferred to the familiar sequences in the test phase. Furthermore, the segmentation pattern of the practiced sequences transferred to the mirrored sequences. For example, Figure 4.3 shows that the relapse at the third key of the familiar sequence, executed with the left hand is transferred to the mirrored sequence, executed with the right hand. Planned comparisons performed on the third key of familiar and mirrored sequences showed an interaction between Hand and Condition, $F(1,17)=13.4$, $p=.002$, which indicated the transfer of the relapse at the third key from familiar to mirrored sequences.

The amount of errors decreased during the test phase, $F(2,34)=23.0$, $p<0.001$, $\varepsilon=0.76$. There was a main effect of Key, $F(4,68)=20.9$, $p<0.001$, $\varepsilon=0.48$ (mean PC for Key 1 to Key 5, respectively 92.8, 89.1, 87.3, 83,0, 83.9) and of Condition, $F(2,34)=8.7$, $p=.001$ (mean PC for familiar, mirrored and unfamiliar sequences, respectively 90.4, 88.2, 83.0). Planned comparisons were performed and indicated that participants produced less errors with mirrored than with

unfamiliar sequences (F(1,17)=8.9, p=.008) and less errors with familiar than with unfamiliar sequences (F(1,17)=13.7, p=.002), but no differences were found on the amount of errors between familiar and mirrored sequences (F(1,17)=1.7, p=.2). The interaction between Block and Condition indicates that the differences in PC between the conditions decreased with practice (F(4,68)=3.8, p=0.25, ε=0.59), the interaction between Block and Key showed that the difference in PC between blocks increased from Key 1 to Key 5 (F(8,136)=4.1, p=.01, ε=0.39) and the interaction between Condition and Key showed that the difference in PC between conditions increased from Key 1 to Key 5 (F(8,136)=4.4, p=.003, ε=0.53).
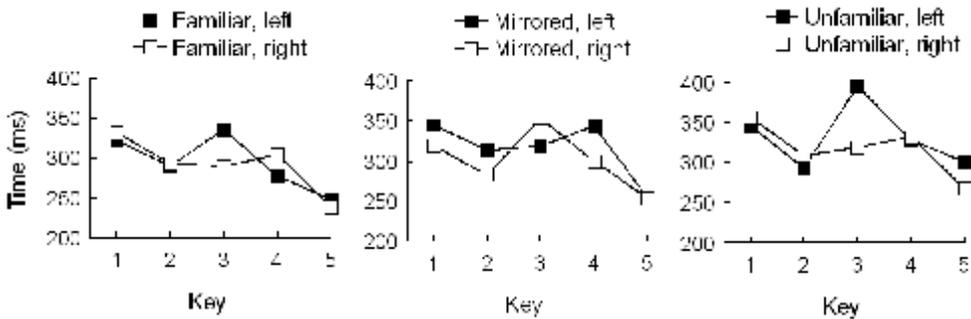

Figure 4.3 Mean response time in the test phase as a function of Condition, Key and Hand.

Summarizing, participants became faster during the test phase and made less errors during the test phase. Furthermore, the differences between the keys within a sequence in RT and PC decreased during the test phase and the differences between the conditions in RT and PC decreased during the test phase, which together indicates that the sequences were still learned in the test phase. More importantly, familiar sequences were executed faster than mirrored sequences and mirrored sequences were executed faster than unfamiliar sequences, which produced most errors. Finally, chunking was more pronounced in the left hand than in the right hand. Most importantly, chunking of familiar sequences in the practice phase transferred to the familiar sequences in the test phase and chunking transferred from the left hand to the mirrored right hand.

EEG analyses
In the present study the baseline was set at the 100 ms before the first stimulus, whereas the baseline in our previous study (De Kleine & Van der Lubbe, in preparation-a) was set 100 ms before the go/nogo interval (during which the last stimulus was still present). In order to check if there were conditional differences between these two time-points in activity an ANOVA with time (2), Condition (3)

and Hand (2) was performed on the amplitudes measured at Cz. There was no main effect of Condition, $F(2.34)=0.4$, $p=.7$, and there was no interaction between Time and Condition, $F(2,34)=1.3$, $p=.3$. Therefore, the effects found in our previous study were probably not caused by differences in attention paid to the stimuli in the different conditions.
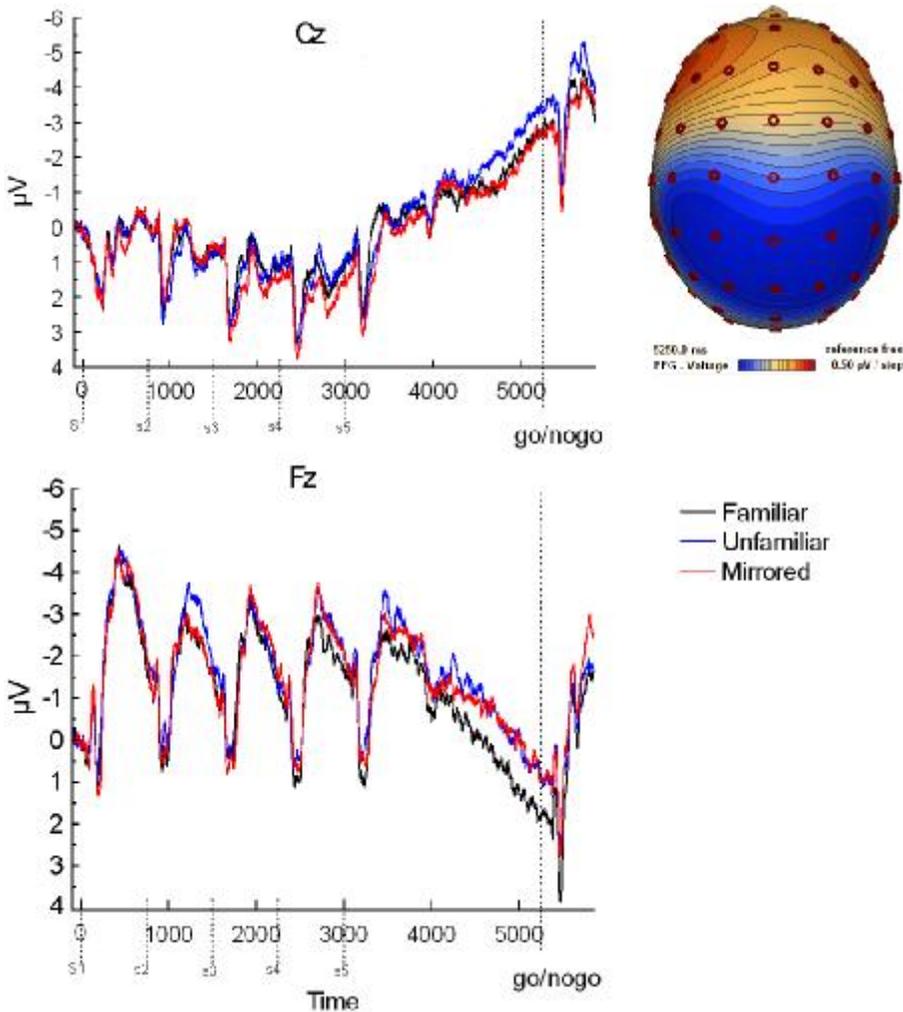

Figure 4.4 Left: event-related brain potentials at Cz and Fz as a function of Condition. Right: topographic map of the go/nogo-signal of the grand average across conditions.

The CNV waveform determined on Cz as a function of Condition is displayed in Figure 4.4. The CNV was increased for unfamiliar sequences as

compared with mirrored and familiar sequences. Statistical analyses performed on the 1200-0 ms interval prior to the go/nogo stimulus revealed that negativity increased over time (mean amplitude for the 200ms time intervals from -1200 to 0 ms before the go/nogo, respectively -1.4, -1.0, -1.2, -1.5, -2.1, -2.7), $F(5,85)=13.7$, $p=0.001$, $\varepsilon=0.22$. Furthermore, one-sided testing showed a significant interaction between Time and Condition $F(10,170)=2.3$, $p=.037$, $\varepsilon=0.36$. This interaction showed that negativity increased with time, which was most pronounced for unfamiliar sequences and less pronounced for familiar and mirrored sequences (see Figure 4.4) However, planned comparisons showed no significant differences between conditions in CNV amplitude for the 1200 ms interval before the go/nogo-signal; familiar vs. unfamiliar, $F(1,17)=2.0$, $p=.2$, mirrored vs. unfamiliar, $F(1,17)=1.6$, $p=.2$, familiar vs. mirrored, $F(1,17)=0.1$, $p=.8$.

The CNV waveform determined on Fz as a function of Condition is displayed in Figure 4.4. The CNV was increased for familiar sequences as compared with mirrored and unfamiliar sequences. Statistical analyses performed on the 1200-0 ms interval prior to the go/nogo stimulus revealed that negativity increased over time (mean amplitude for the 200ms time intervals from -1200 to 0 ms before the go/nogo, respectively -0.6, -1.0, -0.6, -0.2, 0.3, 0.9), $F(5,85)=56.7$, $p<0.001$, $\varepsilon=0.30$. Furthermore, one-sided testing showed a marginal significant interaction between Time and Condition $F(10,170)=2.0$, $p=.057$, $\varepsilon=0.35$. This interaction showed that negativity decreased with time, which was most pronounced for familiar sequences and less pronounced for unfamiliar and mirrored sequences (see Figure 4.4). However planned comparisons showed no significant differences between conditions in CNV amplitude for the 1200 ms interval before the go/nogo-signal; familiar vs. unfamiliar, $F(1,17)=3.2$, $p=.09$, familiar vs. mirrored, $F(1,17)=3.5$, $p=.07$, mirrored vs. unfamiliar, $F(1,17)=0.1$, $p=.8$.
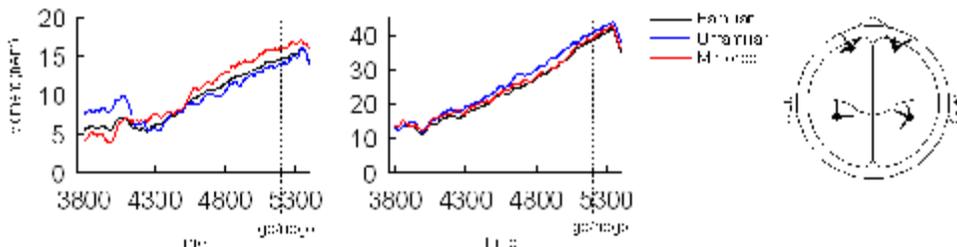

Figure 4.5 Left: Source waveforms of the left, central regional source for each condition. Middle: Source waveforms of the left, frontal regional source for each condition. Right: estimated source model for preparation-related activity for the 800-0 ms interval before the go/nogo-signal for the grand average across conditions.

Source analyses were performed in order to determine the likely brain areas from which CNV activity originates. Since the CNV increased during the preparation interval the time window from -800 to 0 ms before the go/nogo-signal was most appropriate for our fitting procedure, similar to our previous study. PCA showed that one component accounted for 98.9 % of the variance of familiar sequences, 99.1 % of the variance of unfamiliar sequences and for 98.7 % of the variance of mirrored sequences. Since left and right handed responses were given bilateral activity was expected, therefore symmetrical source pairs were fitted. Furthermore, since a quantitative rather than a qualitative difference in general motor preparation between unfamiliar, familiar and mirrored sequences was expected we fitted source pairs on the grand average of all three conditions. Two symmetrical source pairs were fitted given that adding an additional source hardly lowered the RV and the source waveforms showed minimal activity. Subsequently the source model was applied to each condition, after which the RV amounted to 8.5 % for familiar sequences, 7.0 % for unfamiliar sequences and 7.8 % for mirrored sequences. Figure 4.4 displays obtained source locations in the -800 to 0 ms before the go/nogo-signal. Although spatial resolution of the source localization is limited, it is suggested that one symmetrical source pair is localized around the central sulcus and one symmetrical source pair in the frontal lobe. Furthermore, Figure 4.5 shows the source waveforms of the left, central regional source and the left frontal regional source of each condition. The source waveform of the left, central regional source is highly similar for each condition, but the source waveform of the left, frontal regional source is increased for mirrored sequences, compared with unfamiliar and familiar sequences. This suggests more frontal activity for mirrored sequences compared with familiar and unfamiliar sequences.

4.4 Discussion

In the present study, we questioned whether the effector independent representation (a GMP), is in a general motor format or in an abstract format. Familiar, unfamiliar and mirrored sequences were prepared and executed using the go/nogo DSP task. In line with Grafton et al. (2002) and Verwey and Clegg (2005) it was expected that the execution of mirrored sequences would be slower than familiar sequences and faster than unfamiliar sequences. We focus on sequence preparation, since sequence preparation can give a better view on the precise function of the processes underlying sequences as compared with motor execution, as execution of a sequence is contaminated with the preparation of forthcoming responses. Furthermore, sequence preparation is thought to rely on similar processes as sequence execution. The CNV, a measure derived from the

EEG was used to study the covert preparation processes, which reflects general motor preparation. A general motor representation implies an identical CNV for familiar and mirrored sequences, since the CNV reflects general motor preparation. In contrast, an abstract representation implies an identical CNV for unfamiliar and mirrored sequences, since, in this case the sequence will be new at a motor level. Furthermore, if segmentation patterns transfer from the practiced to the mirrored sequence, we suggest that the underlying representation includes a temporal component. Finally, we wanted to see if we could replicate the CNV result of a previous study, which showed an increased CNV for unfamiliar sequences as compared with familiar sequences (De Kleine & Van der Lubbe, in preparation-a), suggesting more general motor preparation before unfamiliar sequences than before familiar sequences.

As expected, behavioral results showed that mirrored sequences executed with the unpracticed hand were executed faster than unfamiliar sequences and slower than familiar sequences. This shows, for the first time, that in the DSP task there is transfer to mirrored sequences. This agrees with Grafton et al. (2002) and Verwey and Clegg (2005), who suggested that the execution of mirrored sequences includes the same representation as the original sequence and that additional processes are recruited to perform the transformation. Furthermore, it was shown that the relapse at key 3 (probably indicating chunking) transferred from the practiced to the mirrored sequence, which indicates that segmentation patterns transfer from practiced to mirrored sequence. This is a new finding, which suggests that the representation used includes both spatial and temporal aspects. These results indicate that the representation underlying mirrored sequences is effector independent (a GMP), which includes the segmentation pattern of a sequence. Thus, segmentation is already present at a general motor level, which transfers to other effectors.

Figure 4.4 shows an increased CNV at Cz for unfamiliar sequences as compared with familiar and mirrored sequences, suggesting a decreasing need for general motor preparation with practice. A significant interaction between Condition and Time was shown, however, no significant differences were found at Cz between the conditions in the 200 ms before the go/nogo-signal. The small number of trials per conditions could be the possible cause of the lack of significance differences between conditions. However, since Figure 4.4 shows identical CNV amplitude at Cz for familiar and mirrored sequences, it is suggested that the effector independent representation is probably motoric in nature. This general motor preparation could be used for both the execution of familiar sequences executed with the practiced hand and of mirrored sequences executed with the unpracticed hand, without additional transformations. Furthermore, this general motor preparation was increased for unfamiliar sequences, as compared with

familiar and mirrored sequences. This suggests that the activity of the GMP decreases with practice, which suggests that with unfamiliar sequences response specifications are unknown and have to be filled in, whereas with familiar and mirrored sequences more response specifications are fixed in the GMP. This agrees with Grafton et al. (2002) and Verwey and Clegg (2005), who suggested that the execution of mirrored sequences includes the same representation as the original sequence. It could be that with more extensive practice this general motor representation also becomes hand specific or that the effector dependent representation comes on top of the effector independent representation, in that the effector dependent representation is mechanically adjusted to the used effectors, as was suggested by Verwey and Wright (2004) and Verwey and Clegg (2005). However, future research needs to clarify this.

Furthermore, Figure 4.4 shows an increased CNV at Fz for familiar sequences as compared with unfamiliar and mirrored sequences, though, the differences between conditions at Fz were only marginally significant. Again, the small number of trials per conditions could be the possible cause of the lack of significance differences between conditions. However, since Figure 4.4 shows identical CNV amplitude at Fz for unfamiliar and mirrored sequences, it was suggested that more planning was required for the preparation of unfamiliar and mirrored sequences as compared with familiar sequences, as the prefrontal cortex is involved in the representation, planning and memory of actions (Fuster, 2001; Koechlin & Jubault, 2006; Ashe et al., 2006; Willingham, 1998). This suggests that the prefrontal cortex may be involved in the transformation of the mirrored sequence. Furthermore, since the difference between the conditions remains until the go/nogo signal, it is expected that the prefrontal cortex is involved in the memory of the mirrored action.

In relation to underlying brain mechanisms, source localization showed that the CNV originated from motor areas and frontal areas. This agrees with observations that motor areas, like the primary motor cortex and the supplementary motor areas, are involved in the temporal organization of sequences (Tanji, 1994; Kennerley, Sakai, & Rushworth, 2004; Verwey, Lammens, & Van Honk, 2002). Furthermore, this agrees with observations that the prefrontal cortex is involved in the representation, planning and memory of actions (Fuster, 2001; Koechlin & Jubault, 2006; Ashe, Lungu, Basford, & Lu, 2006; Willingham, 1998) and is highly active during new movement sequences and not active when execution becomes automatic (Jenkins, Brooks, Nixon Frackowiak, & Passingham, 1994). Source localization showed similar source waveforms for the central regional source across conditions, whereas the source waveform for the frontal regional source was increased for mirrored sequences compared with familiar and unfamiliar sequences. This suggests that the prefrontal cortex is more active with mirrored

sequences than during familiar and unfamiliar sequences, which could mean that the prefrontal cortex is involved in transferring of the practiced sequence to the mirrored sequence. This agrees with Grafton et al. (2002) and Verwey and Clegg (2005), who suggested that the execution of mirrored sequences includes the same representation as the original sequence, reflected in the CNV, and that additional processes are recruited to perform the transformation, reflected in the frontal source.

Furthermore, Figure 4.4 shows an increased CNV for unfamiliar sequences, as compared with familiar sequences, which agrees with result of our previous study (De Kleine & Van der Lubbe, in preparation-a). This suggests more general motor preparation before unfamiliar sequences than before familiar sequences. We suggest that, with practice, as sequences become learned, chunks are prepared at a general motor level instead of individual responses. However, some studies suggest that the CNV is, in addition to general motor preparation, an index for endogenous attention (Gómez, Flores, & Ledesma, 2007). This suggests that in the present study participants paid less attention to stimuli of familiar sequences, than to stimuli of unfamiliar sequences. This seems realistic, since participants already know after a few stimuli of the familiar which sequence is presented (as it is familiar), whereas with unfamiliar sequences participants have to pay attention to all stimuli, as the sequence is unknown to them. This could be an alternative explanation of the CNV effect in the present study. However, source localization of the CNV showed a motor source, whereas endogenous attention is thought to rely on the parietal cortex. Furthermore, the CNV is also thought to reflect the readiness to respond, since the CNV is related to the readiness potential, which displays greater negativity over the motor cortex contralateral to the responding hand in case of voluntary hand movements. In relation to the present study, increased readiness to respond might be expected for familiar sequences as compared with unfamiliar sequences. However, the results of the present study show an increased CNV for unfamiliar sequences, as compared with familiar sequences. Overall, this suggests that in the present study the CNV reflects general motor preparation rather than increased readiness to respond.

Concluding, in line with findings with the SRT task (Grafton et al., 2002; Verwey & Clegg, 2005) mirrored sequences in the go/nogo DSP task, executed with the unpracticed hand were executed slower than familiar sequences and faster than unfamiliar sequences. Furthermore, segmentation patterns transfer from familiar to mirrored sequences. We suggest that during the preparation of discrete motoric sequences a motoric, effector independent representation is formed, indexed by the CNV, which can be used for practiced sequences executed with the practiced hand and for mirrored sequences executed with the unpracticed hand. Source localization suggested that central motor areas are equally involved

in familiar, mirrored and unfamiliar sequences, whereas a frontal source was increasingly active during mirrored sequences. This may indicate that the general motor representation originates from motor areas, and can be used for familiar and mirrored sequences, whereas additional processes are performed in the frontal cortex to perform the transformation. Finally, the influence of this general motor representation decreases with practice, which could reflect the preparation of chunks instead of individual stimuli.

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5 Motor Learning and Chunking in Dyslexia[*]

Abstract

The present experiment investigated whether dyslexics had problems with executing discrete keying sequences and with switching between chunks within those sequences. Dyslexics and controls executed 2 six-key sequences, with 1 sequence consisted of 2 successive instances of one three-key segment (2x3 sequence) and the other did not involve such a repetition (1x6 sequence). It was assumed that during execution of the 2x3 sequence the same chunk could be reused, whereas during execution of the 1x6 sequence a switch between chunks had to be made. Dyslexics were slower than controls in executing the 1x6 but not in the 2x3 sequence. We suggest that the smaller amount of repetitions of the chunks in the 1x6 sequence or the increased difficulty of the 1x6 sequence led to the slowed execution of the 1x6 sequence in dyslexics.

5.1 Introduction

Dyslexics have difficulties with learning to read, spell and write, despite normal intellectual capacity, adequate sociocultural and educational opportunities and intact sensory abilities (Habib, 2000; Shaywitz, 1998). Approximately 5%-12% of the population is affected by dyslexia (Katusic, Colligan, Barbaresi, Schaid & Jacobsen, 2001). In addition to language problems, dyslexics often suffer from sensory problems unrelated to reading (Eden & Zeffiro, 1998; Habib, 2000; Stein & Walsh, 1997) and have problems with processing rapidly successive information in the auditory and visual domains (Habib, 2000; Hari & Renvall, 2001).

At present there are several theories regarding the cause of dyslexia. The most established theory is the phonological processing theory. This theory states that dyslexia is caused by a deficit at the level of phoneme representation, which leads to difficulties in using and manipulating phonemes when learning to read (Manis et al., 1997). The phonological processing theory only accounts for language related deficits in dyslexics, whereas numerous researchers have found additional problems in dyslexia unrelated to language. For example, researchers have found deficits in motor skills (Fawcett & Nicolson, 1999), balance (Nicolson & Fawcett, 1990), low-level visual and auditory processing (Talcott & Witton, 2002), and information processing speed (Nicolson & Fawcett, 1994). The present study

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[*] In press with Journal of Motor Behavior, De Kleine, E. & Verwey, W.B.

investigates the relationship between motor learning and dyslexia. Therefore theories regarding motor deficits in dyslexia will be discussed in more detail.

One theory regarding motor deficits in dyslexia is the temporal processing theory. This theory suggests that different impairments that dyslexics show - for example in language, visual, and sensorimotor tasks - all stem from a fundamental deficit in the processing of rapidly changing stimuli or rapidly successive stimuli (Habib, 2000; Tallal, Stark & Mellits, 1985). Auditory experiments have suggested that for the typical dyslexics' problems with reading, writing and spelling are caused by difficulties with the perception of rapid acoustic elements in human speech (Tallal & Piercy, 1973, 1975; Tallal et al., 1985). A related hypothesis, the cerebellar-deficit hypothesis, attributes timing problems in dyslexia to cerebellar dysfunction. Indeed, the cerebellum is supposed to play a crucial role in timing and in motor and sequence learning (e.g. Ivry, Keele & Diener, 1988). Previous studies have found support for the cerebellar-deficit hypothesis by showing timing deficits in dyslexics (Nicolson, Fawcett & Dean, 1995) and by showing a diminished activation of the cerebellum in dyslexics during motor learning (Jenkins, Brooks, Nixon, Frackowiak & Passingham, 1994; Nicolson et al., 1999). Nicolson & Fawcett (2000) showed that even after extended practice dyslexics are slower and more prone to error on a keyboard spatial task and on a choice response task. Nicolson & Fawcett's (2001) finding supports the cerebellar-deficit hypothesis, which suggests difficulties with both new and well-learned motor skills in dyslexics. In addition, the cerebellum is thought to be responsible for the ability to establish associations between stimuli and responses and to be linked to implicit sequence learning (Menghini, Hagberg, Caltagirone, Petrosini & Vicari, 2006), which suggests that dyslexics have difficulties especially when learning is implicit. In conclusion, the temporal processing theory states that dyslexics have difficulties with the processing of rapidly changing stimuli or stimuli presented in rapid succession. The cerebellar-deficit hypothesis attributes these problems in dyslexia to the cerebellum and suggests problems with timing, motor learning and implicit sequence learning.

In this regard, a second hypothesis regarding motor deficits in dyslexia, the sluggish attentional shifting (SAS) hypothesis, is interesting because it suggests that dyslexics have difficulty with the disengagement of attention once their attention is engaged (Hari & Renvall, 2001). The SAS hypothesis suggests that because of disengagement problems, dyslexics prolong chunks and have difficulties with switching between chunks. Chunking is a process of segmentation or reorganization that results in a reduced number of information units, called chunks. For example, a telephone number is more easily remembered as 06-23-24-25, than as 0-6-2-3-2-4-2-5. In this way, regularly used large quantities of

information can be segmented or reorganized in practical units in order to overcome short-term memory limitations.

Therefore, the cerebellar-deficit hypothesis suggests problems with learning sequential movements occur because of timing difficulties, whereas the SAS hypothesis suggests problems with learning sequential movements occur because of difficulties with attention disengagement. A frequently used task for investigating learning of sequential movements is the serial response time (SRT) task. In the SRT task, participants react to a spatial cue by pressing the spatially corresponding key. Unbeknownst to participants, on some blocks the stimuli are presented in a particular sequence. Participants will generally respond more quickly when the stimuli are presented in a sequence than when stimuli are presented pseudorandomly, even if participants cannot explicitly report the sequence and thus rely on implicit knowledge (Willingham, Nissen & Bullemer, 1989). Previous studies have shown mixed results of the SRT task in dyslexics. Some researchers found sequence learning deficits with the SRT task in dyslexics (Howard, Howard, Japikse & Eden, 2006; Nicolson et al., 1999; Menghini et al., 2006; Stoodley, Harrison & Stein, 2006; Vicari et al., 2005; Vicari, Marotta, Menghini, Molinari & Petrosini, 2003), whereas others did not (Rüsseler, Gerth & Münte, 2006; Kelly, Griffiths & Frith, 2002; Waber et al., 2003). Still, other studies suggested that dyslexics have difficulties with implicit sequence execution and not with explicit sequence execution (Vicari et al., 2003; Rüsseler et al., 2006). Rüsseler et al. (2006) suggested that the lack of sequence learning deficits in dyslexia found in some studies with the SRT task was caused by the development of explicit knowledge with some versions of the SRT task.

In the present study, we used the discrete sequence production (DSP) task, which gave us the opportunity to study chunking (Verwey & Dronkert, 1996; Rhodes, Bullock, Verwey, Averbeck & Page, 2004). In a typical DSP task, participants practice two discrete sequences by responding to series of three to six key-specific stimuli. All but the first stimuli are presented immediately after the response to the previous stimulus. Dyslexics and controls practiced two DSP sequences, one consisting of two successive instances of one three-key segment (2x3 sequence) and the other did not involving such a repetition (1x6 sequence; Verwey, Lammers & van Honk, 2002). In the present study, we imposed chunking during practice by inserting a variable response-stimulus interval (RSI) between the third and fourth key of both sequences (Verwey, 1996). The RSI induced a sequence with two identical three-key chunks (2x3 sequence) and a sequence with two non-identical three-key chunks (1x6 sequence). Compared with the frequently used SRT task, the DSP task was characterized by a small number of keypresses per sequence and more repetitions per sequence. Ultimately, with practice, key-dependent cues are no longer needed, because the first cue acts as an imperative

stimulus for the entire sequence (Verwey, 1999). We investigated whether dyslexics experience difficulties with executing DSP sequences. The cerebellar-deficit hypothesis suggests difficulties in dyslexia during the initial stages of sequence learning and less problems with practice (Nicolson & Fawcett, 2000). In addition, we examined whether dyslexics have problems with switching between chunks within sequences. The cerebellar-deficit hypothesis suggests that dyslexics are slowed on both the 2x3 and the 1x6 sequence, because of an automatization deficit which is unrelated to chunking. The SAS hypothesis predicts that dyslexics are only slowed on the 1x6 sequence, as a switch between two different chunks has to be made.

5.2 Method

Participants
Participants were 40 students from the University of Twente and the Saxion College, including 19 dyslexics (12 men and 7 women) and 21 nondyslexics (11 men and 10 women). All were right-handed and between 18 and 28 years old. The dyslexics had a documented history of the condition, as was shown by an official medical report. The dyslexics were paid €24 for their participation, whereas the controls received course credits for their participation. All participants were right-handed according to Annett's handedness inventory (Annett, 1970), were native speakers of Dutch, and signed informed consent before the start of the experiment. There was no difference in handedness between controls and dyslexics (see table 5.1). The ethics committee of the University of Twente approved the study.

Apparatus
We controlled stimulus presentation and response registration with E-Prime version 1.1 on a 2.8 GHz Pentium 4 PC running under Windows XP. Participants were seated in a dimly lit room in front of a 17 inch computer screen with a viewing distance of approximately 60 cm.

DSP Task
Participant placed their right-hand fingers on four keys of a computer keyboard: the index finger on the C key, the middle finger on the V key, the ring finger on the B key and the little finger on the N key of a normal computer keyboard. Four horizontally aligned squares (2.5°) presented in the center of the screen functioned as placeholders for the stimuli. The four horizontally aligned squares subtended 13° and had the same alignment as the four response keys. The squares

presented in silver on a black background and at the start of a sequence the squares were filled with the background color (black). After a 1500 ms interval, one square was filled with yellow, to which the participant reacted by pressing the corresponding key. Immediately after a key press another square filled, and so on. If a participant pressed a wrong key, an error message appeared and the same square was refilled until the correct response was given. With a premature first response, feedback indicated that the response was too early and the 1500 ms-fore-period started again. One sequence involved six key-specific cues, all of which the participant had to react to.

Each participant executed two six-key sequences, one sequence with two successive instances of one three-key segment (2x3 sequence), and one that did not involve such a repetition (1x6 sequence). The sequences appeared in a random order and were combinations of the keys C, V, B, and N. We used the following four combinations of 2x3 and 1x6 sequences with different participants; vnc-vnc and bcn-cbv, bcn-bcn and nvb-vnc, nvb-nvb and cbv-bcn, cbv-cbv and vnc-nvb. Finger-specific effects are largely controlled by using-across participants in each group-each key in each position of the sequence.[1] We instructed participants to react as accurately and fast as possible to each stimulus and we measured response time (RT) from target onset to the next response. Participants practiced the sequences in four blocks of 160 sequences, yielding a total of 320 practice trials for each sequence. The fifth block was the test block, which also comprised 160 sequences. During practice, the RSI between the third and fourth key of all sequences varied randomly between 0, 200, 400 and 600 ms to enforce the same segmentation across participants. In the test block, the RSI between all keys was 0 ms. Halfway through every block there was a break for 20 s, during which the participant could relax. During this break and at the end of each block the participants received feedback about their mean RT and the number of errors since the previous feedback. Every practice block was followed by a short break of approximately 2 minutes, and we offered a break of at least 10 minutes between blocks 2 and 3.

Procedure and Design
Before starting the experiment, we presented participants with the Dutch version (translation of the English version) of the Dyslexic Screening Test (DST; Fawcett & Nicolson, 1996; Kort et al., 2005). The DST includes a test of single-word reading, spoonerism, spelling, verbal working memory, writing, two tests of rapid naming,

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[1] The number of participant did not allow perfect counterbalancing. However, removing four participants in the analyses in order to achieve perfect counterbalancing did not change the results. Therefore, the number of participants was kept unchanged.

and two tests of phonemic awareness. All tests were paper-and-pencil tests. Subsequently, participants performed the DSP task. After the DSP task, participants filled out a paper-and-pencil questionnaire, which first asked them to recall the practiced sequences (recall test), and then asked them to identify the two sequences (of the 16 sequences) that they had practiced (recognition test).

Data analysis

T1 indicated the time between stimulus onset and depression of the first key. Interkey interval was defined as the time between the onsets of two consecutive keypresses within a sequence (stimulus onset co-occurred with depression of the previous key). The interkey intervals T2-T6 preceded keypresses 2 through 6 and executing one sequence denoted a trial. We excluded from analysis the first two trials of every block, the first two trials after every break, and trials in which one or more errors had been made. We also eliminated from the analysis those sequences in which the sequence execution time-the sum of the six response times in a sequence-lasted longer than the mean sequence execution time across participants per group, and within blocks, plus three standard deviations. In this last procedure we removed 1.6 % of the trials (2.5 % for the dyslexics, 0.8% for the controls). We analyzed the number of sequences in which one or more errors had been made was analyzed. However, we did not use the total number of errors, as one error in a sequence could easily lead to additional errors in subsequent keypresses because of the high execution rate. We did use the Greenhouse-Geisser correction with corrected values of the degrees of freedom whenever the sphericity assumption of the F-test was violated.

5.3 Results

Dyslexia tests

We analyzed scores of the dyslexia tests using a multivariate analysis of variance (ANOVA). A significant difference between the groups was found on dyslexia test performance, $F(9,30)=4.6$, $p<.005$. Table 5.1 shows the univariate tests comparing groups' scores on the dyslexia tests. It appears that dyslexics scored significantly worse on the tests of picture naming, letter naming, reading, spelling, the tests of phonemic awareness (nonsense sentences), and writing, whereas there were no significant differences between the groups on the spoonerism test and the verbal working memory test.

	Dyslexic	Range	Control	Range	p-Value
Dyslexia Screening Test					
Picture Naming	35.53 (9.3)	25-69	30.29 (3.9)	25-40	0.023
Letter Naming	20.53 (4.5)	15-33	16.62 (3..0)	11-22	0.002
Reading	44.21 (10.6)	29-71	32.10 (6.1)	23-44	<0.001
Spoonerism	8.68 (2.5)	0-11	9.71 (1.4)	6-11	n.s.
Spelling	30.16 (3.6)	22-34	34.57 (1.3)	31-36	<0.001
Working memory	6.32 (1.9)	3-11	6.24 (1.6)	4-10	n.s.
Nonsense sentences A	78.42 (4.0)	70-83	81.48 (2.3)	76-83	0.005
Nonsense sentences B	129.95 (45.3)	71-235	66.10 (17.0)	43-109	<0.001
Writing	26.68 (5.3)	13-36	32.10 (3.9)	22-37	0.001
Annett's Handedness	19.32 (4.9)	8-24	19.33 (3.7)	11-24	n.s.
Recall 2x3	5.79 (0.9)	2-6	6.00 (0.0)	6-6	n.s.
Recall 1x6	5.53 (1.02)	3-6	5.90 (0.4)	4-6	n.s.
Recognition 2x3	1.00 (0.00)	1-1	0.95 (0.2)	0-1	n.s.
Recognition 1x6	0.95 (0.23)	0-1	0.95 (0.2)	0-1	n.s.

Table 5.1 Mean scores, SD (in parentheses) and range for each group and significance (p-value) of the difference between both groups of each dyslexia screening part-test, handedness test, recall tests and recognition tests.

Practice phase

Figure 5.1 shows the results of performance on the DSP task by Sequence and Group. We evaluated RTs using repeated-measures ANOVA with the variables Block (1-4), RSI (0, 200, 400 or 600 ms), Sequence (2x3 or 1x6) and Key (T1-T6) as within-subjects variables and Group (Dyslexics or Control) and Version (1-4) as between-subjects variables. During the practice blocks the difference in response time between the 2x3 sequence and the 1x6 sequence was larger for dyslexics than for controls, as was shown by the significant interaction between Sequence and Group, $F(1,31)=5.7$, $p<.05$. There was no significant difference in RT across sequences, between groups during the practice phase, $F(1,31)=2.7$, $p>.1$. Furthermore, we performed a repeated-measures ANOVA with Block (1-4) and Sequence (2x3 or 1x6) as within-subjects variables and Group (dyslexics or control) as between-subjects variable on error rates to investigate group differences in the practice phase. More errors were made during the 1x6 sequence than during the 2x3 sequence, $F(1,38)=8.0$, $p<.01$ (11.3 vs. 9.3 %, respectively)

and dyslexics made more errors than controls, $F(1,58)=5.1$, $p<.05$ (12.1 vs. 8.6 %, respectively).
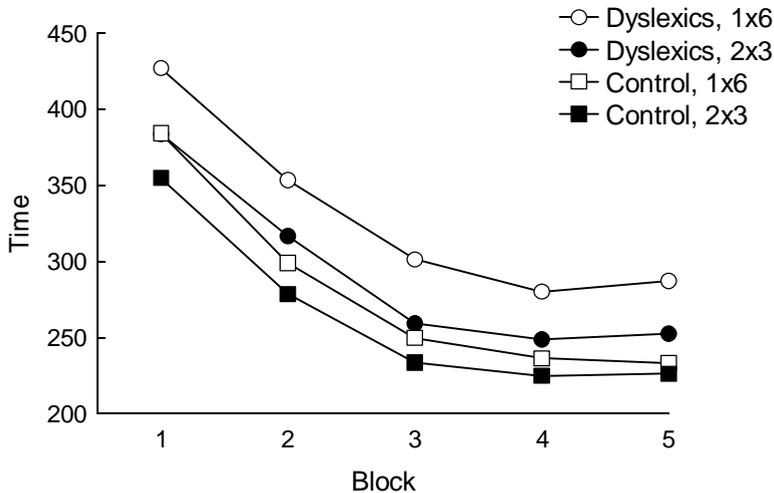

Figure 5.1 Mean RT in the 1x6 and 2x3 sequence for dyslexics and controls as a function of Block.

Test phase

We performed a repeated-measures ANOVA on RT with Sequence (2x3 or 1x6) and Key (T1-T6) as within-subjects variables and Group (dyslexics or control) and Version (1-4) as between-subjects variables to investigate group differences in the test phase when RSI was 0 ms. A trend emerged that showed that dyslexics are slower compared with controls, $F(1,32)=3.9$, $p=.058$. A significant interaction between Sequence and Group, $F(1,32)=11.1$, $p<.005$ showed that the difference in response time between the 2x3 sequence and the 1x6 sequence was larger for dyslexics than for controls (see Figure 5.1). Planned comparisons showed a significant difference between dyslexics and controls for the 1x6 sequence, $F(1,32)=6.7$, $p<.02$, and no difference between the groups for the 2x3 sequence, $F(1,32)=1.6$, $p>.2$.

To investigate if there were differences between the sequences in the initiation of the sequence, the execution of the chunk, and chunk transition, we performed an additional ANOVA with the variable Phase (initiation à Key 1; execution à mean Key 2, 3, 5 and 6; and transition à Key 4). We found no significant interaction was found between Phase, Group and Sequence, $F(2,76)=0.5$, $p>.5$ or between Phase and Group, $F(2,76)=0.8$, $p>.4$. Last, we performed repeated-measures ANOVA on error rates with Sequence (2x3 or 1x6)

as within-subjects variable and Group (dyslexics or control) as between-subjects variables to investigate group differences in the test phase. It was shown that dyslexics made more errors than controls, $F(1,38)=4.7$, $p<.05$ (14.7 vs. 10.0 %, respectively). Therefore, we did not observe any indications that transitions were slowed more in dyslexics than execution.

Recall and recognition test

Table 5.1 shows the results of the recall and recognition tests for the two groups, per sequence. For recall the maximum score was six, as six keys could be recalled correctly. Controls had a perfect recall score for the 2x3 sequence (mean 6) and a nearly perfect score for the 1x6 sequence (mean 5.90). Dyslexics had a mean recall score of 5.79 and 5.53, respectively for the 2x3 and the 1x6 sequence. For recognition, the score was either one or zero, respectively, and correct or incorrect, respectively. Controls had a mean recognition score 0.95 for both the 2x3 and 1x6 sequence, and dyslexics had a mean recognition score of 1 and .95 for the 2x3 and 1x6 sequence, respectively. We found no significant differences between the groups in the mean recall and recognition test for both sequences (see Table 5.1). Their nearly perfect recall score suggests that explicit knowledge had developed to the same extent in both groups.

5.4 Discussion

The goal of the present experiment was to investigate if dyslexics would have problems with executing learned movement sequences, and specifically with switching between chunks within sequences. Seven out of nine subtests of the dyslexia test battery showed significant differences between the dyslexics and controls, confirming that the dyslexics could be classified as such. The verbal working-memory test did not yield significant differences between the groups and therefore verbal working-memory capacity can be excluded as possible reason for group differences.

The DSP task involved two sequences, the 2x3 and 1x6 sequence. The differences between the two sequences were that (a) the 2x3 sequence had the same chunk repeated, which leads to double exposure, and (b) the 1x6 sequence included a shift between two different chunks, which was more difficult than a shift between two identical chunks. Results showed that dyslexics were slower than controls in executing the 1x6 sequence, but not so in executing the 2x3 sequence. As this slowing was found at all sequence positions, there seems to be a general problem with executing the 1x6 sequence, rather than a chunk transition problem as predicted by the SAS-hypothesis. The cerebellar-deficit hypothesis suggests

that dyslexics would initially be slower in executing both keying sequences, but with practice less slowing was suggested. This was not confirmed either, as only the 1x6 sequence was slowed in dyslexics in the test phase. We suggest that the smaller number of repetitions of the chunks in the 1x6 sequence or the increased difficulty of the 1x6 sequence led to the slowed execution of the 1x6 sequence in dyslexics. Further research needs to clarify the reason for the slowing of the 1x6 sequence in dyslexics. Still, a trend was shown in the test phase, indicating that overall dyslexics were slower than controls in sequence execution. We observed a similar trend during the practice phase; though not evident in the ANOVA. These two trends of slowing in participants with dyslexia indicate that, overall, dyslexics were slowed in sequence learning compared with controls, which agreed with the automatization deficit in dyslexics that Nicolson and Fawcett (1990) suggested, which is also in line with the cerebellar-deficit hypothesis. Nicolson and Fawcett argue that dyslexics have a deficit related to automatization in all modalities and in all tasks, and thus also in gross and fine motor skills. These automatization deficits are thought to be related to a cerebellar deficit (Nicolson, Fawcett, & Dean, 1995), for which behavioural and neuroanatomical evidence was found (Fawcett, Nicolson, & Dean, 1996; Finch, Nicolson, & Fawcett, 2002; Nicolson et al.,1995).

Last, recall rates showed that all participants had developed explicit knowledge of the sequences. Previous research showed that both implicit and explicit sequence mechanisms are involved in parallel during sequence learning (Jiménez & Méndez, 2001; Willingham & Goedert-Eschmann, 1999). For the DSP task it could be hypothesized that initially, when participants respond to key-specific cues, execution relies on implicit knowledge. With practice, the implicit knowledge was repeated so many times that participants become aware of the repeating sequence, which led to explicit mechanisms becoming more important. Furthermore, with additional practice, as execution speed increases, implicit mechanisms become more important again, as execution becomes automatic. If the slowed execution of the 1x6 sequence in dyslexics is related to the amount of practice of chunks, then it is possibly related to the reliance on implicit and explicit mechanisms underlying sequence learning. Future research needs to clarify this.

In conclusion, the present experiment showed that dyslexics were slower than controls in executing the 1x6 sequence, but not so in executing the 2x3 sequence. The slowing in the 1x6 sequence could not be related to the chunk transition within the sequence. We suggest that the smaller number of repetitions of the chunks in the 1x6 sequence or the increased difficulty of the 1x6 sequence led to the slowed execution of the 1x6 sequence in dyslexics in the test phase.

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6 Sequence learning in dyslexia: Evidence for an automatization deficit in motor skill[*]

Abstract

De Kleine and Verwey (2009b) observed reduced performance in dyslexics with sequences with two different chunks (1x6 sequence) compared with sequences consisting of two completely identical chunks (2x3 sequence). The present study revealed that with the same amount of practice per chunk in 2x3 and 1x6 sequences, dyslexics were slower than controls, on both sequences. Furthermore, a motor-buffer span task showed no differences between dyslexics and controls. These findings suggests that the reduced performance of 1x6 sequences in dyslexics (De Kleine & Verwey, 2009b) had been caused by insufficient practice of each chunk, and not by a higher motor-buffer capacity requirement. It was concluded that dyslexics have difficulties with the automatization of skills, irrespective of sequential structure.

6.1 Introduction

The most prevalent developmental disorder is dyslexia, affecting 5-12 % of the population. Dyslexia is characterized by difficulties to read, spell and write, despite normal intellectual capacity, adequate sociocultural and educational opportunities, and intact sensory abilities (Habib, 2000; Shaywitz, 1998). These characteristics of dyslexia have led to the formulation of the phonological core deficit hypothesis. However, recent research suggests that in addition to language problems, dyslexics also experience problems in other domains, for example in the speed of information processing and the development of motor skills.

A theory regarding impairments in dyslexia broader than phonology, accounting for deficits in visual and sensory-motor tasks, is the temporal processing theory. According to this theory, the different impairments in dyslexics all stem from a fundamental deficit in the processing of rapidly changing stimuli or rapidly successive stimuli (Habib, 2000; Tallal, Stark, & Mellits, 1985). Results of auditory experiments support the view that the typical problems of dyslexics with reading, writing and spelling are caused by difficulties with the perception of rapid acoustic elements in human speech (Tallal & Piercy, 1973, 1975; Tallal et al., 1985).

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[*] In preparation, De Kleine, E.

Somewhat in line with the temporal processing theory, Nicolson and Fawcett argued that dyslexics have a deficit related to automatization in all modalities and in all tasks, and thus also in gross and fine motor skills (Nicolson & Fawcett, 1990; Fawcett & Nicolson, 1992). They showed that dyslexics have deficits in postural stability (Fawcett & Nicolson 1999; Fawcett, Nicolson, & Dean, 1996), in the automatization of skills (Nicolson & Fawcett, 1990), in time estimation (Nicolson, Fawcett, & Dean, 1995), in speeded performance (Nicolson & Fawcett, 1994), and in eye blink conditioning (Nicolson, Daum, Schugens, Fawcett, & Schulz, 2002). These automatization deficits are thought to be related to a cerebellar deficit (Nicolson, Fawcett, & Dean, 1995, 2001), for which behavioral, neuroimaging and neuroanatomical evidence was found (Fawcett et al., 1996; Finch, Nicolson, & Fawcett, 2002; Nicolson et al., 1999). Previous studies found support for the cerebellar-deficit hypothesis, by showing diminished activation of the cerebellum in dyslexics during motor learning (Nicolson et al., 1999). Nicolson and Fawcett (2000) showed that even after extended practice, dyslexics are still slower and more error-prone on a keyboard spatial task (Pacman game), and on a choice response task. Furthermore, implicit sequence learning has been linked to the cerebellum, which may explain why dyslexics experience difficulties in implicit learning tasks (Menghini, Hagberg, Caltagirone, Petrosini, & Vicari, 2006).

De Kleine and Verwey (2009b) examined whether dyslexics had problems with executing learned movement sequences and especially with switching between chunks within those sequences. A discrete sequence production (DSP) task was used, which gave the opportunity to study chunking (Verwey & Dronkert, 1996; Rhodes, Bullock, Verwey, Averbeck, & Page, 2004). In a typical DSP-task two discrete sequences are practiced by responding to series of three to six key-specific stimuli. All (but the first) stimuli are presented immediately after the response to the previous stimulus. Dyslexics and controls practiced two DSP sequences, one consisted of two non-identical three-key segments (1x6 sequence) and one sequence consisted of two successive instances of one three-key segment (2x3 sequence) (Verwey, Lammers, & van Honk, 2002). Chunking was imposed during practice, in all sequences, by inserting a response-stimulus interval (RSI) between the third and fourth key of the sequence, which varied randomly between 0, 200, 400 and 600 ms, (Verwey, 1996). This resulted in one sequence of two non-identical chunks (1x6) and one sequence of two identical chunks (2x3). Results showed a clear segmentation of the sequences. Furthermore, the results showed that dyslexics were slower than controls in executing the 1x6 sequence, but not so in executing the 2x3 sequence. As this slowing was found at all sequence positions, there seems to be a general problem with executing the 1x6 sequence rather than a chunk initiation/transition problem. A chunk transition problem would cause a relapse at the fourth key of the 1x6 sequence, as a switch

between chunks had to be made between the third and fourth key of the 1x6 sequence. Thus, execution of the chunk in the 2x3 sequence, which was practiced twice as much, was not slowed in dyslexics, while the 1x6 sequence was.

De Kleine and Verwey (2009b) argued that either less practice of the chunks in the 1x6 sequence and/or the increased difficulty of the 1x6 sequence, compared with the 2x3 sequence, led to the slowed execution of the 1x6 sequence in dyslexics. The 1x6 sequence was more difficult than the 2x3 sequence, as a transition between two different chunks had to be made in the 1x6 sequence, whereas the 2x3 sequence consisted of a repetition of two identical chunks. The transition between two different chunks leads to an increased load on the motor-buffer capacity, as two chunks had to be stored, whereas in the 2x3 sequence only one chunk had to be stored in the motor-buffer. In the present study I investigated if the slowed execution of the 1x6 sequence in dyslexics was caused by either the amount of learning, or the length of the sequence. Participants performed a modified DSP-task, in which the chunks of the 1x6 and 2x3 were practiced equally much, and a motor-buffer span task.

In the current DSP-task, I examined whether the difference in execution time of the 1x6 sequence between control and dyslexics remains when the amount of practice is the same for each chunk. To make the 1x6 sequence and the 2x3 sequence as similar as possible, I used the same segments to build both sequences. Participants practiced two 3-key sequences (A, B). In the test phase, the two practiced sequences were combined into 6-key sequences, which resulted in two sequences with two different chunks (1x6 sequence à AB, BA) and in two sequences with two identical chunks (2x3 sequence à AA, BB). A go/nogo DSP-task was used, in which participants know before execution what sequence is to be executed (see De Kleine & Van der Lubbe, in preparation-a). In this task, key-specific stimuli are presented in succession, followed by a go/nogo-signal. After a go-signal, participants react as fast and accurately as possible by pressing the corresponding keys. This go/nogo DSP-task made it possible to give the 1x6 and 2x3 sequences the same amount of practice. If the slowed execution of the 1x6 sequence in dyslexics was caused by the amount of practice per segment in the study of De Kleine and Verwey (2009b), then no additional slowing in the 1x6 sequence, as compared with the 2x3 sequence, was expected in dyslexics in the present study, since the amount of practice per segment was the same for both sequences. The typical DSP-task was not used, since possible differences between the 1x6 and the 2x3 sequence would only be visible during the last keypresses (in the present task the first three keys are never unique to any sequence), which was not desirable.

In addition, three memory span tests were performed. First, in a motor-buffer span task, I examined whether an assumed increased requirement of motor-

buffer capacity resulted in reduced performance for dyslexics. To vary the requirement of motor-buffer capacity of sequences a go/nogo DSP-task was used in which the length of the sequences was manipulated. Previous studies have shown that movement sequences are executed more slowly with increasing sequence length, which is referred to as the sequence length effect on latency (slower execution of the first key of the sequence) and the sequence length effect on rate (slower execution of later keys in the sequence) (Monsell, 1986; Sternberg, Monsell, Knoll & Wright, 1978; Verwey, 2003). The sequence length effect on latency is thought to be due to the preparation of a whole sequence before response initiation (Kennerley, Sakai, & Rushworth, 2004). This preparation is thought to consist of the selection and programming of individual responses or motor chunks (Verwey, 2003). However the programming and execution of keys within sequences occurs in parallel; the programming of movement sequences is not entirely finished before initiation, but can be distributed before and during sequence execution (e.g. Van Galen & Weber, 1998; Rosenbaum, Hindorff, & Munro, 1987; Verwey & Eikelboom, 2003). In line with distributed programming, the sequence length effect on rate is thought to be due to individually different segmentation patterns, which results in a few long interkey intervals at different positions, and thus increases average execution rate. This segmentation is in line with the distributed programming view, as chunks can be prepared during the execution of a previous chunk. Thus, it is expected that longer sequences are executed more slowly, as more (distributed) programming is needed. Thus, if the difference in requirement of motor-buffer capacity between 1x6 and 2x3 sequences caused the slower execution of the 1x6 sequence in dyslexics in the study of De Kleine and Verwey (2009b), then dyslexics are expected to have reduced performance when executing sequences with greater sequence length.

       Furthermore, previous studies found visuospatial working-memory deficits in dyslexia (Smith-Spark, Fisk, Fawcett, & Nicolson, 2003; Smith-Spark & Fisk, 2007). To examine if dyslexia is related to a problem with motor memory or to a more general memory problem, possible group differences in visuospatial working-memory were studied. The Corsi Block test (Corsi, 1972; Milner, 1971) was administered, which measures visuospatial span, which reflects an individual's visuospatial working-memory capacity. If a general memory problem underlies dyslexia, this would also be visible in a visuospatial span task. Finally, verbal working-memory span was measured in the Dyslexia Screening Test (DST). If a general memory problem was responsible for the group differences, then it should be visible in the verbal working memory task.

6.2 Method

Participants
Participants were 40 students (age 18-40) from the University of Twente and the Saxion College, including 20 dyslexics (10 men and 10 women) and 20 nondyslexics (6 men and 14 women). 38 participants were right-handed, one was left-handed and one was ambidextrous according to Annett's handedness inventory (Annett, 1970). The dyslexics had a documented history of the condition, as was shown by an official medical report. The dyslexics were paid €30 for their participation, while the controls received course credits for their participation. All participants were native speakers of Dutch and signed informed consent before the start of the experiment. The ethics committee of the University of Twente approved the study.

Apparatus
We controlled stimulus presentation and response registration with E-Prime version 1.1 on a 2.8 GHz Pentium 4 PC running under Windows XP. Participants were seated in a dimly lit room in front of a 17 inch computer screen with a viewing distance of approximately 60 cm.

Procedure
On the first day, participants performed the Dyslexia Screening test (DST) and subsequently the discrete sequence production (DSP) task (practice and test phase). On the second day, participants performed the Corsi Block test and subsequently the motor-buffer span task.

DSP-task
Participant placed their right-hand fingers on four keys of a computer keyboard: the index finger on the C key, the middle finger on the V key, the ring finger on the B key and the little finger on the N key. The presentation of the stimuli is displayed in Figure 6.1. Four horizontally aligned squares presented in the center of the screen functioned as placeholders for the stimuli (2.5°). The four horizontally aligned squares subtended 13° and had the same alignment as the four response keys. The squares were presented in silver on a black background and at the start of a sequence the squares were filled with the background color (black). After 1000 ms a square was filled yellow for 400 ms, next, the second square was filled yellow for 400 ms, until a third (practice phase) or a sixth square (test phase) was presented. Next, the default screen, with the four horizontally aligned squares filled with black, was presented for 750 ms. After this interval, the fixation-plus was colored either red (5%) or blue (95%). A red fixation-plus stayed on the screen for 3000 ms and

indicated that no action was to be executed (nogo trial). A green fixation-plus (for 100 ms) indicated that participants had to start pressing the buttons corresponding to the presented sequence of yellow squares. Feedback on the accuracy of the responses was given after producing a response sequence. A false alarm signal was presented when participants reacted before the go/nogo-signal.
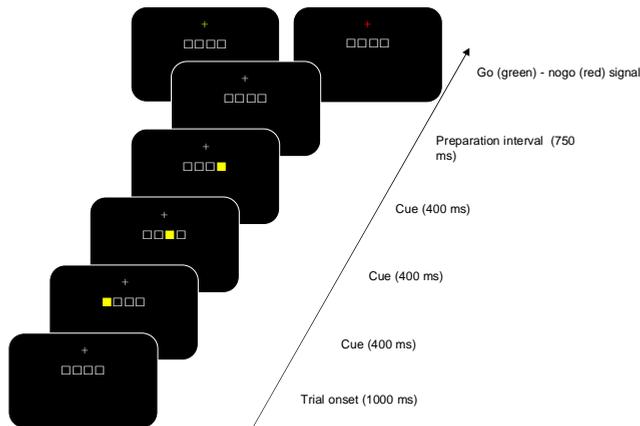

Figure 6.1 An example of the sequence of stimuli from the start of a trial until the go/nogo-signal. The duration of each stimulus frame is indicated along the time axis.

During the practice phase, each participant executed two three-key sequences and during the test phase, each participant executed four six-key sequences, which were all four combinations of the two practiced three-key sequences. This resulted in two sequences with two successive instances of one three-key segment (2x3 sequence) and two sequences which did not involve such a repetition (1x6 sequence). The sequences appeared in a random order and were combinations of the keys C, V, B, and N. We used the following three-key sequences during practice; VNC, BCN, NVB, and CBV, which were counterbalanced over participants. This amounted to four versions of two combinations (two versions were dropped to avoid two identical sequential keys in the test phase, namely VNCCBV and BCNNVB). Finger-specific effects were controlled by using-across participants in each group-each key in each position of the sequence. We instructed participants to react as accurately and fast as possible to the go stimulus and measured response time (RT) from target onset (go) to the ensuing response and as the time between two successive key-presses.

In the DSP-task participants practiced the sequences in four blocks of 160 sequences, yielding a total of 320 practice trials for each three-key sequence. The fifth and sixth block were test blocks, each consisting of 80 sequences, yielding a total of 40 repetitions of each sequence. Halfway through every block there was a break for 20 s, during which the participant could relax. During this break and at the end of each block the participants received feedback about their mean RT and the number of errors since the previous feedback. Every practice block was followed by a short break of approximately 2 minutes, and we offered a break of at least 10 minutes between Blocks 2 and 3.

Span tasks

The motor-buffer span task I developed was highly comparable to the DSP-task, except that a number of squares were successively filled with yellow for 750 ms (instead of 400 ms), 91 % of the time a go-trial was given and 9% of the time a nogo-trial was presented (instead of 5%). Furthermore, during the motor-buffer span task only random sequences were presented, in which a stimulus was never immediately repeated. The random sequences increased in length from four to six keys. In the motor-buffer span task sequences were presented in six blocks of 80 sequences. The first two blocks consisted of four-key sequences, the third and fourth block consisted of five-key sequences and the final two blocks consisted of six-key sequences. Halfway through every block there was a break for 20 s during which the participant could relax. During this break and at the end of each block the participants received feedback about their mean RT and the number of errors since the previous feedback. Every block was followed by a short break of approximately 2 minutes and a break of at least 10 minutes was given between Blocks 2 and 3.

In the Corsi Block test (Corsi, 1972; Milner, 1971) participants were presented 18 different sequences of illuminated squares which had to be memorized and recalled, by indicating their locations. Sequence length increased from 2-9 squares and two sequences were given for each sequence length. The value of the participants' span was determined by the length of the highest correct sequence he/she was able to reproduce.

We presented participants with the Dutch version (translation of the English version) of the DST (Fawcett & Nicolson, 1996; Kort et al., 2005). The DST includes a test of single-word reading, spoonerism, spelling, verbal working memory, writing, two tests of rapid naming and two tests of phonemic awareness. All tests were paper-and-pencil tests.

Data analysis

In the DSP-Task T1 indicated the time between stimulus (go-signal) onset and depression of the first key. The interkey interval was defined as the time between the onsets of two consecutive keypresses within a sequence. The interkey intervals denoted T2-T6 preceded keypresses 2-6 and executing one sequence denoted a trial. We excluded from analysis the first two trials of every block, the first two trials after every break, and trials in which one or more errors had been made. We also eliminated from analysis those sequences in which the sequence execution time- the sum of the three or six RTs in a sequence-lasted longer than the mean sequence execution time across participants per group, and within blocks, plus 3 standard deviations. In this last procedure removed 1.4% of the trials of the practice phase (controls and dyslexics respectively 1.2 and 1.6 %), and 2.3% of the trials of the test phase (controls and dyslexics respectively 0.6 and 4.4 %). We did use the Greenhouse-Geisser correction with corrected values of the degrees of freedom whenever the sphericity assumption of the *F*-test was violated.

Scores of the DST were analyzed using a multivariate analysis of variance. Results of the Corsi Block test were analyzed with a *t*-test. RTs and percentage correct (PC) of motor-buffer span task were evaluated by a repeated-measures ANOVA with Sequence Length (4, 5 or 6) as within-subjects variable and Group (dyslexics or control) as between-subjects variable. RTs and PC of the practice phase of DSP-task were evaluated by a repeated-measures ANOVA with the variables Block (1-4) and Key (T1-T3) as within-subjects variables and Group (Dyslexics or Control) as between-subjects variable. RTs and PC of the test phase of DSP-task were evaluated by repeated-measures ANOVA with the variables Sequence (1x6 or 2x3) and Key (T1-T6) as within-subjects variables and Group (Dyslexics or Control) as between-subjects variable.

6.3 Results

Span and dyslexia tests

Dyslexics scored significantly lower on the DST than controls, $F(9,30)=4.3$, $p=.001$. Table 6.1 shows the univariate tests comparing groups' scores on the DST. It appears that dyslexics scored significantly worse on the tests of rapid naming, single-word reading, spelling, spoonerism, one test of phonemic awareness, and writing, $Fs(1,38)>5.6$, $ps<.025$, but not on another test of phonemic awareness and the verbal working-memory test, respectively, $F(1,38)=2.4$, $p=.127$ and $F(1,38)=.07$, $p=.409$. Furthermore, a t-test showed that there was no significant difference between dyslexics and controls on the Corsi Block test, $t(38)= -1.329$, $p=.192$. Finally, the motor-buffer span task showed that controls made less errors

than dyslexics (15 vs. 22.3 %), $F(1,38)=4.8$, $p=.035$, which was also somewhat visible in RT, $F(1,38)=3.0$, $p=.092$, indicating that controls executed the sequences faster than the dyslexics (328 vs. 386 ms). However, there was no interaction between Group and Length on RT ($F(2,76)=1.1$, $p=.319$) or on PC ($F(2,76)=2.0$, $p=.154$). Thus, the reduced performance of dyslexics on the 1x6 sequences in the previous study can not be explained by differences in verbal working-memory, visuospatial and motor-buffer span between dyslexics and controls.

	Dyslexic	Range	Control	Range	p-Value
Picture Naming	9.30 (3.10)	2-14	12.50 (2.14)	7-16	.001
Letter Naming	8.80 (3.07)	4-14	12.50 (2.98)	5-16	.001
Reading	8.60 (2.14)	5-13	11.05 (1.96)	6-13	.001
Spoonerism	8.20 (2.17)	5-12	10.00 (2.64)	6-13	.024
Spelling	8.70 (2.56)	1-12	11.30 (1.78)	8-15	.001
Working memory	10.70 (2.00)	7-14	10.15 (2.16)	5-14	n.s.
Nonsense sentences A	9.00 (3.58)	3-13	10.50 (2.37)	7-13	n.s.
Nonsense sentences B	8.90 (2.02)	5-12	12.55 (1.99)	10-16	<.001
Writing	10.40 (3.07)	5-16	13.85 (2.54)	8-17	<.001

Table 6.1 Mean scores and SD (in parentheses) of the dyslexia screening test (DST). *p*-values indicate the significance of group differences (dyslexics vs. controls).

DSP-task -Practice phase
In the practice phase dyslexics were slower than controls (273 vs. 214 ms), $F(1,38)=6.1$, $p=.017$, and made more errors than controls (5.8 vs. 1.8 %), $F(1,38)=8.1$, $p=.007$, but improvement did not differ.

DSP-task -Test phase
Figure 6.2 shows the mean RTs of the test phase of DSP-task in dyslexics and controls as a function of Key. In the test phase dyslexics were slower than controls (273 vs. 228 ms), $F(1,38)=4.5$, $p=.041$, and dyslexics made more errors than controls (9.7 vs. 4.0 %), $F(1,38)=6.3$, $p=.017$. Furthermore, there was an interaction between Key and Group on RT, $F(5,190)=3.0$, $p=.032$. Planned comparisons showed that, across groups, Key 4 was significantly slower than the mean of key 2, 3 , 5 and 6, $F(1, 38)=55.7$, $p<.001$. Furthermore, planned comparisons showed that the difference between Key 4 and the mean of key 2, 3, 5, and 6 is larger for controls than for dyslexics, $F(1,38)=6.2$, $p=.02$, indicating that the execution of chunks is causing the slowed execution in dyslexics. The three-way interaction between Sequence, Key and Group on RT was not significant, $F(5,190)=1.2$,

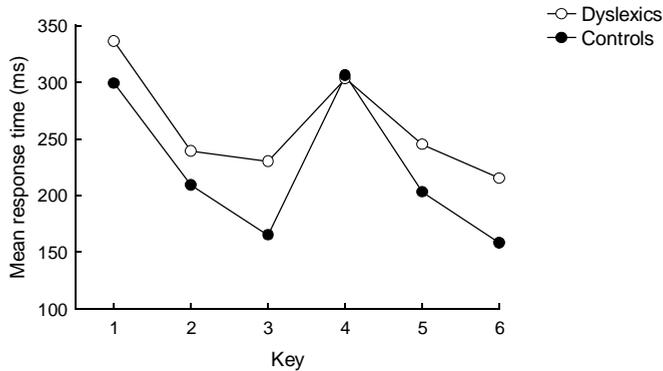p=.314, indicating that the interaction between Key and Group was significant for 1x6 and 2x3 sequences.

Figure 6.2 Mean RT in the test phase of DSP-task in dyslexics and controls as a function of Key.

6.4 Discussion

Seven out of nine subtests of the DST showed significant differences between dyslexics and controls, confirming that the dyslexics were correctly classified. The verbal working-memory test of the DST, the Corsi Block test and the motor-buffer span task did not yield significant differences between the groups. Therefore verbal working-memory, visuospatial and motor-buffer span capacity cannot account for observed group differences.

The DSP-task examined whether there was a difference in execution time between the 1x6 and the 2x3 sequence in dyslexics when the amount of practice per chunk was identical. If the amount of practice per chunk had caused slower execution rate of the 1x6 sequence in the study of De Kleine and Verwey (2009b), then no additional slowing in dyslexics was expected in the 1x6 sequence compared with the 2x3 sequence in the present study. Results showed that dyslexics were slower and produced more errors than controls. However, no interaction between Group and Sequence was found, which shows that dyslexics were slowed to the same degree in the 1x6 and 2x3 sequences. Thus, with an identical amount of practice per chunk both sequences are slowed in dyslexics, but there was no difference in slowing between sequences. This indicates that in the study of De Kleine and Verwey (2009b), the slowed execution of the 1x6 sequence in dyslexics, as compared with the 2x3 sequence, was caused by the reduced amount of practice of the chunks in the 1x6 sequence. This supports the notion

that dyslexics have a general problem with learning and executing motoric sequences, especially when practice is limited.

Results of the study of De Kleine and Verwey (2009b) showed that the difference between the 1x6 and the 2x3 sequence in controls decreases with practice, whereas the difference stays the same in dyslexics. Thus, controls overcome the smaller amount of practice in the 1x6 sequence, whereas the dyslexics did not. This suggests that with a standard DSP-task, different processes are involved in the learning of the 1x6 sequence in controls and dyslexics, when a 2x3 sequence is learned in parallel.

It could be that the problem in dyslexics with the execution of motor sequences is related to implicit learning (Howard, Howard, Japikse, & Eden, 2006; Menghini, et al., 2006; Rüsseler, Gerth, & Munte, 2006). Previous research indicated that both implicit and explicit sequence mechanisms are involved in parallel during sequence learning (Jiménez & Méndez, 2001; Willingham & Goedert-Eschmann, 1999). In addition, Cleeremans and Jiménez (2002) distinguish three stages in the formation of internal representations during skill acquisition; implicit, explicit and automatic representations. The early stage of skill acquisition involves implicit representations. At this stage representations are not very strong and distinctive and therefore control over representations at this stage is low. The second stage involves explicit representations, which are well defined and over which one can exert control. The third stage involves automatic representations, which become so strong that their influence on behavior can no longer be controlled easily. For the DSP-task this suggests that initially, when participants primarily respond to key-specific cues, execution relies on implicit knowledge (Stage 1). With practice the implicit knowledge has been applied so often that participants become aware of the repeating sequence which leads to explicit mechanisms becoming more important (Stage 2). Furthermore, with additional practice, as execution speed increases, execution becomes automatic (Stage 3).

Based on the three stages of Cleeremans and Jiménez (2002) it could be hypothesized that in the study of De Kleine and Verwey (2009b) control participants automatically executed the 1x6 and 2x3 sequences (Stage 3), while dyslexics automatically executed the 2x3 sequence (Stage 3), but relied on explicit representations when executing the 1x6 sequence (Stage 2). Furthermore, it can be suggested that in the present study controls and dyslexics automatically executed the 1x6 and 2x3 sequences (Stage 3). This suggests that in controls the automatization of sequencing skill spreads over all sequences, irrespective of the amount of practice, whereas with dyslexics automatization is limited to sequences with sufficient practice. This suggests that dyslexics need practice with a specific sequence to attain automaticity, whereas controls need practice with a 'similar'

sequence to attain automaticity. This suggestion agrees with the cerebellar-deficit hypothesis suggesting that dyslexics have problems with skill automatization (Menghini, et al., 2006). The present study can not differentiate between reliance on implicit and explicit representations.

A point of consideration concerns the use of a go/nogo DSP-task in the present study, while the study of De Kleine and Verwey (2009b) used a standard DSP-task. It is possible that the present go/nogo DSP-task relies more on memory than the standard DSP-task. Therefore, faster execution of the 1x6 sequence in dyslexics in the present study compared with the study of De Kleine and Verwey (2009b) may be caused by greater reliance on memory. However, the execution rate of the 1x6 sequence in controls is not increased in the present study as compared with the study of De Kleine and Verwey (2009b). Furthermore, memory span tasks showed no differences between dyslexics and controls. Therefore, the greater reliance on memory in the present go/nogo DSP-task seems not due to the faster execution of the 1x6 sequence.

Furthermore, the present go/nogo DSP-task showed that in dyslexics, across sequences, Key 2, 3, 5 and 6 were slowed as compared to Key 4. This shows that chunk execution was slowed in dyslexics, but chunk initiation/transition was not. This indicates that execution and initiation/transition of chunks rely on different mechanisms. It could be hypothesized that the automatization deficit in dyslexics is most pronounced during the most automatic keypresses and therefore chunk execution is slowed in dyslexics and chunk initiation/transition is not. Furthermore, the cerebellar-deficit hypothesis (Nicolson, Fawcett, & Dean, 2001) attributes problems in dyslexia to cerebellar dysfunction, therefore it could be suggested that chunk execution relies on the cerebellum, whereas chunk initiation/transition does not.

Concluding, the present tasks showed that dyslexics were slower than controls in executing the go/nogo DSP-task, but no differences were found between the 1x6 and 2x3 sequences. Verbal working-memory, visuospatial and motor-buffer span tasks showed no differences between dyslexics and controls. This suggests that the reduced performance of dyslexics executing the 1x6 sequence in the study of De Kleine and Verwey (2009b) was related to the amount of practice per chunk and not to the required motor-buffer capacity. This confirms the hypothesis that, in agreement with the cerebellar-deficit hypothesis, dyslexics have difficulties with the automatization of motor skills (Nicolson & Fawcett, 1990).

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7 Summary and conclusions

Movement can be considered as a crucial aspect of any living being, and has sometimes been considered as the main reason for the actual coming into existence of cognition. Most actions we perform in everyday life consist of series (sequences) of simple movements, by which we are able to attain fluent execution of more complex movement patterns. In this thesis, the mechanisms underlying motor sequence learning, as studied with the discrete sequence production (DSP) task, were investigated by focusing on response times, error rates and EEG measures.

Since sequence learning entails different phases, it is suggested that different representations underlie sequential learning. In chapter 2, we focused on the spatial features of representations underlying sequencing skill in the DSP task. We investigated if the position of the used effector was relevant for the effector-dependent representation. We manipulated the hand used and the position of the hand relative to the body. The data showed that with practice an effector-dependent component develops in parallel with an effector-independent component. Furthermore, the data showed that hand position appeared relevant for execution with the practiced hand. This supported the notion that several representations underlie the execution of motor sequences, one being a representation that is both effector and position dependent. Overall, the results of this study agree with the idea that sequence learning in the DSP task is initially based on stimulus-response learning, but with practice sequence learning in the DSP task becomes based on multiple representations, which develop with practice. We showed that during initial practice an effector-independent representation develops and with additional practice an effector dependent representation develops, which is position dependent.

A discrete sequence can already be prepared before execution. Sequence preparation is thought to include the same processes as sequence execution. Studying sequence preparation can give a clearer view on the precise function of the processes underlying than studying motor execution, since measures of execution of a sequence are contaminated with the preparation of forthcoming responses. Given that preparation is covert, measures derived from the EEG appear especially useful to study movement preparation. In chapter 3, we investigated if the different phases of sequence learning were already visible in the EEG during preparation of sequences. Fixed series of keypresses, familiar and unfamiliar, had to be prepared and executed/withheld after a go/nogo-signal. Results showed an increased contingent negative variation (CNV) and contralateral delay activity (CDA) for unfamiliar sequences as compared to familiar sequences,

but a comparable lateralized readiness potential (LRP) for familiar and unfamiliar sequences. Furthermore, source localization on the CDA showed that the difference of lateralized activity between the preparation of familiar and unfamiliar sequences originated from posterior sites, whereas both the LRP and the CNV related activity originated from motor areas. This observation suggests that the demand on general motor preparation and visual-working memory was increased before unfamiliar sequences. We argue that with familiar sequences, chunks of stimuli are kept in visual-working memory and chunks of responses are preset at a motor level, whereas with unfamiliar sequences individual stimuli are memorized and preset.

General motor preparation suggests a general motor program which can be used by different effectors. Well-known is that a movement, such as writing your name, can be executed by different effectors. This is thought to rely on a common, effector-independent representation (a generalized motor program). In chapter 4 we questioned if the effector-independent representation, underlying sequence learning, is in a general motor format or in a more abstract (spatial) format. We replicated the study of chapter 3, and extended this study by including a condition in which mirrored sequences were prepared and executed with the unpracticed hand. It was predicted that if the effector-independent representation was in a general motor format, it could be used for practiced sequences executed with the practiced hand and for mirrored sequences executed with the unpracticed hand, as the homologue fingers of the unpracticed hand are used. Results showed that mirrored sequences were executed slower than familiar sequences and faster than unfamiliar sequences. This suggests that the same motor representation underlies mirrored and practiced sequences, but that additional processes are recruited to perform the transformation. More importantly, the segmentation pattern of the practiced sequences transferred to the mirrored sequences. These results indicate that an effector independent representation underlies mirrored sequences, which includes spatiotemporal aspects of the sequence. Furthermore, results showed an increased demand on generalized motor preparation, indexed by the CNV, before unfamiliar sequences as compared with familiar and mirrored sequences. This suggests that the representation underlying mirrored and familiar sequences is in a general motor (effector independent) format, such as a general motor program, and not (solely) in an abstract (spatial) format.

To learn more about sequence learning, it is interesting to also study the differences in sequence learning in people with a particular condition, like dyslexia. Dyslexics are thought to have difficulties with skill automatization, such as motor sequence learning. In chapter 5 we investigated if dyslexics have problems with executing discrete keying sequences, and with switching between chunks within those sequences. The cerebellar-deficit hypothesis suggests that dyslexics are

slowed on all sequences, due to an automatization deficit. In contrast, the sluggish attentional shifting (SAS) hypothesis suggests that dyslexics are only slowed on sequences in which a switch between two different chunks has to be made, due to problem with attention disengagement. A reduced performance in dyslexics was shown with sequences with two different chunks (1x6 sequence) as compared with sequences consisting of two identical chunks (2x3 sequence). As this slowing was found at all sequence positions, there seems to be a general problem with executing the 1x6 sequence, rather than a chunk transition problem. We suggest that the smaller amount of repetitions of the chunks in the 1x6 sequence or the increased difficulty of the 1x6 sequence could have been responsible for the slowed execution of the 1x6 sequence in dyslexics. This shows for the first time that dyslexics were slowed in discrete sequence learning, as compared to controls, which agrees with the automatization deficit in dyslexics suggested by the cerebellar-deficit hypothesis.

In chapter 6 we investigated if the smaller amount of repetitions of the chunks in the 1x6 sequence or the increased difficulty of the 1x6 sequence led to the slowed execution of the 1x6 sequence in dyslexics. We observed that with the same amount of practice of chunks in 2x3 and 1x6 sequences, dyslexics were slower than controls, but no differences were found between 1x6 and 2x3 sequences. Furthermore, a verbal working-memory span task, a visuospatial span task and a motor-buffer span task showed no differences between dyslexics and controls. This suggests that the reduced performance of 1x6 sequences in dyslexics was caused by the smaller number of repetitions of the chunks and not by a higher motor-buffer capacity requirement. Thus, with less practice of the chunks in the 1x6 sequence, as compared with the 2x3 sequence, dyslexics are slowed in the 1x6 sequence, as compared with controls. This agrees with an automatization deficit in dyslexics, in line with the cerebellar-deficit hypothesis.

The findings in this thesis are in line with the model of Verwey (2001). This model proposes that the cognitive processor initially selects a representation of a sequence, based on a symbolic, effector-independent representation, and subsequently this sequence is read and executed by the motor processor. It may be that the cognitive processor is responsible for general motor processing and that the motor processor is responsible for effector-specific motor preparation. In line with this, the results of this thesis suggest that initial execution of a sequence induces a high demand on the cognitive processor, as each element in the sequence has to be selected separately, whereas with practice the demand on the cognitive processor will decrease as integrated and complex parts of a sequence (i.e. motor chunks) can be selected at once. Subsequently, the motor chunk, or separate elements in case of initial learning, can be loaded into the motor buffer by the cognitive processor, after which the sequence is executed by the motor

processor. This execution of the sequence is independent of learning, so the demand on the motor processor is identical with practice.

In agreement with the brain model proposed in the general introduction, I suggest that during stimulus-response learning, the prefrontal cortex, involved in the planning of movements, controls the premotor area (PMA). Subsequently, the PMA interacts with the cerebellum in a recurrent loop, which is involved in the timing of rapid movements, the automatization of skills and the establishment of new motor programs. Finally, the PMA sends its information to M1, which generates the neural impulses controlling the execution of movement sequences. In a second phase, during which a new motor program is established, sequence execution becomes under internal control. In this phase, the prefrontal cortex, (planning) and the parietal cortex (spatial coordination of visually presented sequences) send their information to the pre-SMA. Subsequently, the pre-SMA interacts with the basal ganglia in a recurrent loop, which is involved in chunking. Thus, during this second phase, sequence execution is under internal control and sequences get chunked. Furthermore, with additional practice, activation is thought to shift from the pre-SMA to the SMA, which is responsible for the temporal organization of learned sequences. In a final phase, when sequence execution becomes automatic, the role of the prefrontal cortex and the posterior parietal cortex reduce, as the sequence becomes represented at a motor level (M1).

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8 Nederlandse samenvatting

Beweging is een fundamenteel aspect van ieder levend wezen en kan als de belangrijkste reden voor het bestaan van cognitie worden beschouwd. De meeste acties die wij in het dagelijks leven uitvoeren bestaan uit een reeks eenvoudige bewegingen: een bewegingssequentie. Met oefening kunnen deze bewegingssequenties leiden tot een vloeiende uitvoering van complexere bewegingspatronen. Dit proefschrift behandelt de mechanismen die ten grondslag liggen aan het leren van bewegingssequenties (vanaf hier sequenties genoemd). Mechanismen, zoals het opslaan van relevante informatie van sequenties in het geheugen (een representatie) en het segmenteren van sequenties zullen worden behandeld. In de experimenten is de *discrete sequence production task* gebruikt. Hierbij ligt de focus op de analyse van reactietijden, foutenpercentages en maten afgeleid uit het elektro-encefalogram (EEG).

Aangezien het leren van sequenties verschillende fases omvat wordt gesuggereerd dat verschillende representaties ten grondslag liggen aan het leren van sequenties. Hoofdstuk 2 beschrijft een studie waarin de spatiële eigenschappen van representaties, die ten grondslag liggen aan sequenties, zijn onderzocht. Meer specifiek is onderzocht of de positie van de gebruikte effector (hand) relevant is voor de effector-afhankelijke representatie. De hand, gebruikt voor de uitvoering van de sequentie, en de handpositie met betrekking tot het lichaam, werden gevarieerd. De resultaten wijzen erop dat er zich eerst een effector-onafhankelijke representatie ontwikkelt. Vervolgens ontwikkelt er zich een effector-afhankelijke representatie, die ook afhankelijk is van de positie van de effector. Dit ondersteunt het idee dat verschillende representaties ten grondslag liggen aan de uitvoering van sequenties. De resultaten van deze studie zijn in overeenstemming met het idee dat de initiële uitvoering van sequenties gebaseerd is op het leren van stimulus-responsrelaties en met het idee dat met oefening verschillende representaties van sequenties zich ontwikkelen.

Zoals aangetoond verloopt de uitvoering van sequenties in verschillende fases. Verondersteld wordt dat de voorbereiding, net als de uitvoering, ook in verschillende fases verloopt en dat de voorbereiding en uitvoering van sequenties gebaseerd zijn op overeenkomstige processen. Metingen van de uitvoering van een beweging binnen een sequentie kunnen dus worden beïnvloed door de voorbereiding van eerstvolgende bewegingen. De bestudering van de voorbereiding van een gehele sequentie geeft een duidelijker inzicht in de onderliggende processen. Aangezien de voorbereiding van een sequentie niet direct observeerbaar is kunnen maten, afgeleid uit het EEG, hier meer inzicht geven. In de studie beschreven in hoofdstuk 3 wordt onderzocht of de

verschillende fases van het leren van sequenties al zichtbaar zijn tijdens de voorbereiding van sequenties. Vaste sequenties van bewegingen, bekend en onbekend, moesten worden voorbereid en uitgevoerd/onderdrukt na een go/nogo-signaal. De resultaten tonen een verhoogde *contingent negative variation* (CNV) en een verhoogde *contralateral delay activity* (CDA) voor onbekende sequenties in vergelijking met bekende sequenties. Daarnaast tonen de resultaten voor bekende en onbekende sequenties een vergelijkbare *lateralized readiness potential* (LRP). Bronlokalisatie op de CDA laat zien dat het verschil in gelateraliseerde activiteit tussen de voorbereiding van bekende en onbekende sequenties uit posteriore gebieden voortkomt, terwijl zowel LRP- als CNV-gerelateerde activiteit uit motorgebieden voortkomt. Deze resultaten suggereren dat het beroep op algemeen-motorische voorbereiding (geïndiceerd door de CNV) en op visueel-werkgeheugen (geïndiceerd door de CDA) verhoogd is voor onbekende sequenties ten opzichte van bekende sequenties. Verondersteld wordt dat bij bekende sequenties *chunks* (een geheugenspoor waarin meerdere items behandeld worden als een één verwerkingsunit) van stimuli in het visueel-werkgeheugen worden gehouden en *chunks* van reacties op een motorisch niveau gereed worden gezet, terwijl bij onbekende sequenties individuele stimuli worden onthouden en klaargezet.

Algemeen-motorische voorbereiding suggereert een algemeen motorprogramma, welke gebruikt kan worden door verschillende effectoren. Bekend is dat een beweging, zoals het schrijven van je naam, door verschillende effectoren kan worden uitgevoerd. Verondersteld wordt dat dit gebaseerd is op een gemeenschappelijke, effector-onafhankelijke representatie van de beweging: een algemeen motorprogramma. De studie beschreven in hoofdstuk 4 onderzoekt of de effector-onafhankelijke representatie een algemeen-motorisch of een abstract (ruimtelijk) formaat heeft. De studie, beschreven in hoofdstuk 3 is herhaald en uitgebreid door een conditie toe te voegen. In deze conditie werden gespiegelde sequenties voorbereid en uitgevoerd met de ongeoefende hand. Verwacht werd dat een effector-onafhankelijke representatie in een algemeen-motorisch formaat gebruikt kan worden voor geoefende sequenties uitgevoerd met de geoefende hand. Daarnaast werd verwacht dat effector-onafhankelijke representatie in een algemeen-motorisch formaat ook gebruikt kan worden voor gespiegelde sequenties uitgevoerd met de ongeoefende hand, aangezien hier homologe vingers worden gebruikt. De resultaten tonen aan dat gespiegelde sequenties langzamer uitgevoerd worden dan geleerde sequenties, maar sneller dan onbekende sequenties. Dit suggereert dat dezelfde representaties ten grondslag liggen aan gespiegelde en geoefende sequenties, maar dat extra processen nodig zijn om de transformatie uit te voeren. Bovendien laten de resultaten zien dat het segmentatiepatroon van de geoefende sequenties transfereert naar gespiegelde

sequenties. Deze resultaten wijzen erop dat aan gespiegelde sequenties een representatie ten grondslag ligt, die spatiële en temporele aspecten van de sequentie bevat, maar onafhankelijk van de effector is. Verder tonen EEG-maten aan dat onbekende sequenties een verhoogd beroep doen op algemeen-motorische voorbereiding in vergelijking met geleerde en gespiegelde sequenties. Dit suggereert dat dezelfde algemeen-motorische representatie (een algemeen motorprogramma) ten grondslag ligt aan gespiegelde en geleerde sequenties.

Het bestuderen van het leren van een sequentie bij mensen met een stoornis, zoals dyslexie, kan inzicht geven in de processen die ten grondslag liggen aan het sequentieleren. Hoofdstuk 5 beschrijft een studie, waarin onderzocht wordt of dyslectici problemen hebben met het uitvoeren van sequenties en met de wisseling tussen *chunks* binnen sequenties. De *cerebellar deficit hypothesis* voorspelt dat dyslectici op alle sequenties vertraagd zijn vanwege een automatiseringsprobleem. Daarentegen voorspelt de *sluggish attentional shifting hypothesis* dat dyslectici alleen vertraagd zijn bij sequenties waarin een wisseling tussen twee verschillende *chunks* moet worden gemaakt vanwege een probleem met aandachtsverschuivingen. De resultaten van deze studie tonen voor het eerst aan dat dyslectici vertraagd zijn in het uitvoeren van sequenties in vergelijking met controles. Dyslectici laten verminderde prestaties zien op sequenties met twee verschillende *chunks* (1x6-sequenties), vergeleken met sequenties met twee identieke *chunks* (2x3-sequenties). Aangezien alle toetsdrukken binnen de 1x6-sequenties vertraagd zijn, lijkt er een algemeen probleem te zijn met het uitvoeren van de 1x6-sequenties en niet met de wisseling tussen *chunks*. Verondersteld wordt dat de kleinere hoeveelheid herhalingen van de *chunks* in de 1x6-sequenties of de verhoogde moeilijkheid van de 1x6-sequenties de oorzaak is van de vertraagde uitvoering van de 1x6-sequenties bij dyslectici. De resultaten van deze studie zijn in overeenstemming met een automatiseringprobleem bij dyslectici, dat wellicht voorkomt uit een afwijking in (het functioneren van) het cerebellum. De gevonden resultaten komen overeen met de *cerebellar deficit hypothesis*.

In de studie beschreven in hoofdstuk 6 wordt onderzocht of de kleinere hoeveelheid herhalingen van de *chunks* in de 1x6-sequenties en/of de verhoogde moeilijkheid van de 1x6-sequenties heeft geleid tot de vertraagde uitvoering van deze sequenties bij dyslectici. De resultaten van deze studie laten zien dat bij een gelijke hoeveelheid herhalingen van de *chunks* in de 2x3- en de 1x6-sequenties, dyslectici langzamer zijn dan controles. Er zijn geen verschillen gevonden tussen 1x6-sequenties en 2x3-sequenties. Daarnaast tonen testen van verbaal werkgeheugen, visueel-spatieel-geheugen en motorisch geheugen geen verschillen aan tussen dyslectici en controles. Dit suggereert dat de verminderde prestatie op de 1x6-sequenties bij dyslectici, aangetoond in hoofdstuk 5, veroorzaakt wordt door de kleinere hoeveelheid herhalingen van de *chunks* en niet

door een hoger vereiste capaciteit van het motorisch geheugen. Ook de resultaten van hoofdstuk 6 komen overeen met een automatiseringsprobleem van dyslectici, dat wellicht voorkomt uit een afwijking in (het functioneren van) het cerebellum.

De bevindingen beschreven in dit proefschrift stemmen overeen met het model van Verwey (2001). Dit model stelt dat een cognitieve processor een symbolische, effector-onafhankelijke representatie van een sequentie selecteert, welke vervolgens wordt uitgevoerd door de motorprocessor. Verondersteld wordt dat de initiële uitvoering van een sequentie vooral steunt op de cognitieve processor, aangezien elk element in de sequentie afzonderlijk wordt geselecteerd. Met oefening zal de belasting op de cognitieve processor verminderen doordat geïntegreerde, complexe delen van een sequentie (d.w.z. *motorchunks*) meteen worden geselecteerd. *Motorchunks* of afzonderlijke elementen in het geval van het initieel leren, worden in de motorbuffer geladen door de cognitieve processor, waarna de sequentie wordt uitgevoerd door de motorprocessor. De belasting op de motorprocessor wordt verondersteld gelijk te blijven met oefening omdat de uitvoering van de sequentie door de motorprocessor niet afhankelijk is van leren.

Het hersenenmodel, beschreven in de algemene inleiding stelt dat tijdens de initiële stimulus-responsfase van het sequentieleren de *premotor area* (PMA) gecontroleerd wordt door de prefrontale schors (planning). Vervolgens wisselt de PMA informatie uit, via een wederkerige loop, met het cerebellum (timing, automatisering). Tenslotte zendt de PMA zijn informatie naar de *primary motor cortex* (M1), waar de neurale stimuli geproduceerd worden die de uitvoering van sequenties controleren. In de tweede fase van het leren van sequenties, waarin een nieuw motorprogramma wordt gecreëerd, is de uitvoering van sequenties onder interne controle. In deze fase zenden de prefrontaalschors (planning) en de parietaalschors (ruimtelijke coördinatie) hun informatie naar de *pre-supplementary motor area* (pre-SMA), verantwoordelijk voor de temporele organisatie van niet-geleerde sequenties. De pre-SMA wisselt informatie uit, via een wederkerige loop, met de basale ganglia (chunking), en zendt daarna zijn informatie naar de M1. Met extra oefening verschuift de activering van de pre-SMA naar de *supplementary motor area* (SMA), welke verantwoordelijk is voor de temporele organisatie van geleerde sequenties. In de laatste fase van het leren van sequenties, wanneer de uitvoering van sequenties automatisch wordt, wordt de rol van de prefrontaalschors en de parietaalschors minder, aangezien sequenties steeds meer op een motorisch niveau (M1) vertegenwoordigd worden.

Referentie

Verwey, W.B. (2001). Concatenating familiar movement sequences: the versatile cognitive processor. *Acta Psychologica, 106,* 69-95.

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