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IS DISCRETE SEQUENCE LEARNING IMPAIRED IN SCHIZOPHRENIA?

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Foreword

This master thesis was written as a completion to the Master of Science in Psychology: Theoretical and Experimental Psychology. Working on this master thesis for two years has been both exciting and interesting. I learned a lot about sequence learning and schizophrenia, and about my own future goals and interests. Overall, I am very grateful to all the people who supported me throughout this research project, without whom this would have been impossible.

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Abstract

Cognition in schizophrenia is typically characterized by deviant motor functioning, compromising subtle deficits in sensory integration, motor coordination and sequencing of complex motor acts. While many studies have already been devoted to the sequencing of continuous motor acts at an implicit or explicit level, no study has yet investigated discrete sequence skill learning (i.e., the learning of brief and well-defined actions that have a clear beginning and end) in schizophrenia. In the present study, we set out to fill in this gap by using a variant of the discrete sequence production (DSP) task, in contrast to most studies using the serial reaction time (SRT) task to study sequence learning. In the practice phase, patients and controls first became familiar with two movement sequences by responding to two discrete sequences of 6-key specific stimuli. In the ensuing test phase, they executed these two sequences under different conditions, as well as two unfamiliar keying sequences. Our results suggest that there is a significant impairment in discrete sequence learning among people diagnosed with schizophrenia. Moreover, we found that schizophrenic patients were unable to rely on the chunking mode when performing sequences, and instead continued to require external guidance for sequence execution. The present study is the first to demonstrate that schizophrenic patients – in addition to impaired (continuous) implicit and explicit sequence learning – can be impaired in the mastering of discrete motor skills as well. Implications of our results for functional outcomes in the disorder are discussed.

Keywords: schizophrenia; sequence learning; motor skill; discrete sequence production task
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Introduction

In everyday life, people continuously carry out activities which involve complex motor actions. Most of these actions require the rapid execution of a sequence of discrete movements, arranged in a specific and fixed order. In this regard, one might think of motor actions such as writing one’s own name or grabbing a bottle of water. Once the sequence of movements has been learned, the motor action can be performed without too much effort and attentional monitoring, meaning that a sequential motor skill has been acquired (Ruitenberg, Verwey, Schutter, & Abrahamse, 2014). The ability of integrating series of discrete movements into a complex, automated behavior is called sequence learning (Abrahamse, Ruitenberg, de Kleine, & Verwey, 2013), and ensures us that we do not end up with calling a stranger when attempting to type in a familiar phone number or with a mixed up knot when lacing our shoes.

Over the last decades, ample research has been devoted to sequence learning in schizophrenia (Marvel et al., 2007; Pedersen et al., 2008; Siegert, Weatherall, & Bell, 2008) but to our best knowledge these studies all involved the learning of continuous movements, while no study has yet investigated discrete sequence skill learning (i.e. learning sequences of brief, well-defined actions that have a clear beginning and end) in these patients. In the current study, we set out to fill in this gap by examining if and how schizophrenia influences the learning of discrete movements. Moreover, we aim at investigating whether general impairments in discrete sequence skill are manifested in the different execution modes that have been identified in healthy people (Verwey, 1996; Verwey, 1999; Verwey, 2003a; Verwey & Wright, 2004; Verwey & Abrahamse, 2012). Below, we will first discuss schizophrenia in more detail, after which we will describe previous work on sequence learning in both healthy individuals and individuals with schizophrenia. Finally, the present study will be discussed.
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Schizophrenia

During the past century, the precise definition and boundaries of schizophrenia have varied several times (Tandon, Nasrallah, & Keshavan, 2009). Nevertheless, consensus has been reached on the fact that schizophrenia can be considered as a chronic and severe mental disability, characterized by three broad clusters of symptoms, including positive, negative and cognitive symptoms (e.g. Mueser & McGurk, 2004; Rosen et al., 1984). Positive symptoms, such as delusions and hallucinations, reflect an abnormal mental activity which is absent in the healthy population, and result in a loss of touch with reality. One may think, for instance, of people hearing voices that are not physically there. Negative symptoms, on the contrary, indicate the absence of a mental quality which is present in healthy populations. Common negative symptoms include poor speech output (alogia), lack of pleasure in everyday life (anhedonia), lack of initiative or motivation (avolition), and impaired emotional expression (Liddle, 1987). Next to positive and negative symptom clusters, schizophrenia is commonly associated with a bunch of cognitive difficulties such as attention deficits (Cullum et al., 1993; Luck & Gold, 2008), poor executive functioning (Kerns, Nuechterlein, Braver, & Barch, 2008; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009), learning- and working memory deficiencies (Aleman, Hijman, de Haan, & Kahn, 1999; Lee & Park, 2005) and problems with psychomotor speed (Bervoets et al., 2014; Morrens et al., 2008). Many of these cognitive deficits may arise from an impaired ability to represent and maintain contextual information, such as a sequence of prior stimuli or task instructions (Barch, Carter, MacDonald, Braver, & Cohen, 2003; Ford et al., 2010; Hemsley, 2005).

Less recognized, but also well documented in the scientific literature, is the fact that most schizophrenic patients also display a wide range of symptoms characterized by deviant motor functioning (Morrens, Docx, & Walther, 2014). In particular, patients with schizophrenia have been shown to often experience difficulties executing simple repetitive movements, like tapping a rhythm with their hands, or alternately clenching the fist and making a ring with two fingers (e.g. Bombin, Arango, & Buchanan, 2005; Docx et al., 2012). These subtle motor deficiencies are assessed as deficiencies in the sequencing of complex motor acts and are part of the clinical test battery for neurological soft signs (NSS; Chen et al., 1995). NSS generally fall into three clusters, compromising the previously mentioned disorders in the sequencing of complex motor
acts (i.e. the performance of successive movements over a period of time), but also motor coordination (i.e. the performance of several movements simultaneously in time), and sensory integration (i.e. the integration of multisensory information; Docx et al., 2012; Hirjak et al., 2013). In patients diagnosed with schizophrenia, sequencing of complex motor acts is the most frequent problem assessed by NSS and is observed in about one third of the patients (Bombin et al., 2005). This observation, together with the impaired ability to cognitively represent and maintain contextual information in people with schizophrenia, has inspired many researchers to focus on schizophrenic performance in sequencing and to extend sequencing research from the executive to the learning level.

**Sequence Learning**

Sequence learning refers to the acquirement of the skill to relate single movements to each other in a specific order so that rapid and smooth execution of complex movement patterns is attained. Although sequence learning is generally seen as a form of explicit learning, sequence learning paradigms have been used frequently to study implicit learning as well. Indeed, the majority of the sequence learning studies agree upon the notion that sequence learning can develop both implicitly and explicitly (e.g. Honda et al., 1998; Nissen & Bullemer, 1987; Willingham, Nissen, & Bullemer, 1989; Willingham & Goedert-Eschemann, 1999). In general, implicit learning is qualified as an unintentional form of learning that occurs in the absence of awareness, and only exposes itself by improvement at the behavioral level. Explicit learning, on the contrary, is intentional and contains the conscious recall of previously experienced events (Frensch, 1998; Pascual-Leone, Grafman, & Hallett, 1994; Song, Howard Jr., & Howard, 2007). Many studies on the importance of implicit and explicit knowledge in motor-skill learning have focused on the distinction, rather than the integration, of these two types of learning. For example, Nissen and Bullemer (1987) demonstrated that motor skill learning may remain entirely implicit during training. In their study, amnesic patients – who have a severely impaired capacity to learn explicitly – were able to learn a repeating spatial sequence, despite their lack of awareness of the repetition. Similarly, Destrebecqz and Cleeremans (2001) succeeded in disentangling implicit and explicit knowledge by showing that awareness is not always a prerequisite for sequence learning.
One task that has proven to be extremely useful for investigating the acquisition and control of sequential motor skills is the discrete sequence production (DSP) task (e.g. Verwey, 1999). In the DSP task, participants go through sequences involving fixed series of 3 to 7 (typically 6) stimuli. More specifically, a stimulus appears in one of four locations on the screen in a predetermined order, after which the participant has to respond by pressing the spatially corresponding key. Immediately after the correct key is pressed, the next key-specific stimulus is presented. Typically, participants first go through a practice phase in which two sequences of stimuli are repeated over and over again (usually in between 500 and 1000 repetitions per sequence), before going on to the test phase in which half of the trials are composed of a completely novel sequence that acts as control condition.

This design causes participants to make use of two different execution styles. Initially, participants’ responses tend to be determined by the key-specific stimuli, which cause the sequence to be externally driven through online stimulus-response (S-R) translation. However, with practice, participants learn the fixed order of responses and start to execute the whole sequence as soon as they perceive the first stimulus, without the need to attend to the ensuing stimuli in the sequence. This implicates that a DSP task with, for instance, two 6-key sequences now becomes a 2-choice RT task, since the whole sequence is executed as a single response (Verwey, Shea, & Wright, 2015). In other words, practice has led to the development of a sequencing skill, since it caused execution to become more automatic and, moreover, predominantly stimulus-independent.

The more automated phase can be accounted for by the notion of so-called motor chunks that are created during the practice phase. Stated differently, practice leads to the emergence of particular representations that connect a small amount of key responses together into a single representation, called a motor chunk (Leonard & Newman, 1964; Miller, Galanter, & Pribram, 1960; Verwey, 1994). Consequently, these linked responses lend themselves to be selected, initiated and executed as if they were a single motor response (Verwey, 1996), additionally causing sequence-execution to become largely internally driven (Verwey & Abrahamse, 2012). Following practice, typical characteristics of these motor chunks can be studied in the test phase in which unfamiliar (new) sequences are used next to familiar (practiced) sequences.
Another frequently used task to study motoric sequence learning is the Serial Reaction Time (SRT) task (Nissen & Bullemer, 1987). In a typical SRT task, stimulus presentation and response execution are largely identical to the DSP task, however there are some crucial differences. In contrast to the DSP task, SRT-sequences typically involve fixed series of about 12 elements, and there usually is an interval of about 200 ms between the response and the next stimulus. More important even is the fact that the SRT task does not involve discrete motor sequences (i.e., they do not have a clear beginning and end) and that participants are not being informed that the presented stimuli may follow a predetermined order. Learning in the SRT task is demonstrated by participants responding progressively faster with practice, and slowing down when the stimulus order is randomly changed late in training. Since participants may be often unaware of the repeating motor sequence, the SRT task is suited for the study of both explicit (which might occur with longer periods of training, e.g. Willingham, 2001) and – especially – implicit motoric sequence learning. Given that the present study makes use of the DSP task instead of the SRT task, we will go into more detail regarding the typical phenomena, cognitive models and neural bases of discrete sequence learning that have been found with research that uses the DSP task.

**Phenomena in discrete sequence learning.**

Research with the DSP task makes it possible to investigate the mechanisms by which complex real-world actions are achieved and mastered. Moreover, it reveals a number of phenomena that are typically observed in sequence learning, among which (a) the existence of various processing phases of sequence skill (briefly touched upon above), together with the automatic segmentation of longer sequences, and (b) the emergence of explicit sequence knowledge.

According to Abrahamse and colleagues (2013), three different processing phases are involved in the execution of one specific sequence: initiation, execution and concatenation. The first phase – the initiation phase – corresponds to the response time that is associated with the first stimulus in the sequence (i.e. $T_1$; e.g. Verwey & Eikelboom, 2003). As can be seen in Figure 1, this response time is typically much slower than subsequent key presses. This slow start has been explained, in part, by suboptimal temporal anticipation as to when the first stimulus is presented, since the slow $T_1$ is present even when a short and random series of key-presses is carried out.
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Figure 1. Typical pattern of results obtained during the execution of a 6-key sequence in the DSP task. Initiation, execution and concatenation phases are displayed. Importantly, when a sequence contains less elements (< 5 key presses), the concatenation point is usually not observed (Adapted from “Control of automated behavior: insights from the discrete sequence production task,” by E.L. Abrahamse, M.F.L. Ruitenberg, E. de Kleine, and W.B. Verwey, 2013, Frontiers in Human Neuroscience, 7:82)

Following the first key press, responses are much faster. This makes sense since these key presses do not require the selection and preparation processes that already have been fulfilled in the delay between the first sequence element and its response (i.e. T1). As such, these responses only involve execution. However, not all of these execution key-presses are carried out equally fast: in most sequences, a slower response
can be observed about halfway through the sequence (see Figure 1). This abnormality can be explained by the fact that motor chunks have a limited capacity of typically in between four and five key presses. Because of this capacity limitation, longer sequences will be represented by multiple motor chunks (Acuna et al., 2014; Bo & Seidler, 2009; Sakai, Kitaguchi, & Hikosaka, 2003; Verwey, Abrahamse, & Jiménez, 2009). As a result, the upcoming motor chunk has to be retrieved and initiated after finishing the previous one, leading the response time to go up at the concatenation point. Concatenation can be defined as the mechanism that links different motor chunks together so these can be executed smoothly, as if they were one. The concatenation point, then, reflects the change from one chunk to the next.

A second frequently observed phenomenon with respect to sequencing skill, is related to the distinction between implicit and explicit knowledge (see above). Participants in the DSP task are often well-informed about the fact that the response follows a certain predetermined sequence. Together with the saliency of DSP-sequences, this has led to the idea that the DSP task is well-suited for the study of explicit sequence learning (Bo & Seidler, 2009). However, a substantial amount of participants does not acquire explicit and verbalizable sequential knowledge (e.g. elderly have a reduced capacity to develop explicit knowledge, Abrahamse, Ruitenber, Jiménez, & de Kleine, 2011; Gaillard, Destrebecqz, Michiels, & Cleeremans, 2009; Verwey, 2010). At this point, the concepts of structural and judgment knowledge (Dienes & Scott, 2005) come into play: when a participant does not possess explicit knowledge, he is often still able to recognize the fact that there is a certain regularity in the sequence, i.e. judgment knowledge, even when he/she has no knowledge about the structure of a sequence, including its elements, fragments, regularities, abstract patterns etc., i.e., no structural knowledge. The absence of structural knowledge is easier to understand in the context of the SRT task since in this task participants are not informed that the sequence elements follow a predetermined order. In the DSP task, on the contrary, lack of structural knowledge may seem to be more odd, as sequences are typically short and discrete, with participants being informed about the order. Generally, two possibilities have been suggested to underlie this lack of explicit, structural knowledge in the DSP task (Abrahamse et al., 2013). On the one hand, it could be that participants do develop explicit knowledge at the very beginning, but that this
knowledge slowly fades away with practice. On the other hand, it may be that a few participants actually never develop this kind of knowledge, sticking with (at most) implicit knowledge.

**The dual processor model.**

Several cognitive models have been proposed to explain the learning of discrete movement sequence skill. Among them also the dual processor model (DPM), which has been developed in order to explain performance of discrete key-pressing sequences (i.e. performance in the DSP task). Although the DPM is based on research with the DSP task, other discrete sequence learning studies (e.g. studies utilizing little practice of the sequence, sometimes together with the absence of key-specific stimuli or trial-and-error paradigms) can be linked to this model as well, suggesting that the DPM can be viewed as a general model on sequence learning.

**The existence of two processors.** The DPM proposes that a cognitive and a motor processor underlie the execution of discrete movement sequences (Abrahamse et al., 2013; Verwey, 2001; Verwey, Abrahamse, & de Kleine, 2010). Importantly, the relative contribution of each of these processors to sequencing performance is assumed to change with practice, resulting in distinct modes of sequence execution (Verwey, 2003a). When initially performing a motor sequence in the DSP task, the sequence is said to be executed in the *reaction mode*. The idea is that, in this mode, the cognitive processor selects the response that belongs to each element of the sequence, after which it loads those responses into a motor buffer. The motor processor then reads every element stored in the motor buffer in order to execute it. Subsequently, with more practice, execution may shift to the *chunking mode* in which a movement sequence is executed as one or more motor chunks (see above). Motor chunks allow the cognitive processor to select them out of long term memory and load them into the motor buffer, acting as if each motor chunk represents a single response. This allows each element in the motor buffer to be executed in a rapid succession (Verwey, 1999) and participants to perform the sequence in response to just the first stimulus. It is exactly this quickness and automaticity of selecting and executing practiced sequences that represents the sequencing skill.
Recently, indications have been found that discrete keying sequences can also be carried out in a third – intermediate – execution mode, i.e., the associative mode (e.g. Verwey, 2010; Verwey, Abrahamse, Ruitenberg, Jiménez, & De Kleine, 2011; Verwey & Abrahamse, 2012). In this mode, subjects still use the individual sequence elements in order to execute the sequence, yet they already take some advantage from the priming of subsequent reactions by previous responses. This is accomplished by subjects making associations between subsequent events, leading to the emergence of sequence representations (Abrahamse et al., 2013) that are responsible for the priming of successive events.

The model has two additional features. First, it assumes that, after loading in the motor chunks into the motor buffer, the cognitive processor can support the motor processor in the execution of the elements within the motor chunks by translating these key-specific elements into their corresponding response. This leads to a race between two response selection processes: response selection on the basis of the motor processor reading in response-related codes from the motor buffer, and response selection by the cognitive processor selecting responses based on continued S-R translations. This race eventually leads to the fastest possible response by means of statistical facilitation (Verwey, 2001).

As a second additional feature, the loading of each motor chunk into the motor buffer is initially performed by the cognitive processor, yet may become automated for the later motor chunks of a sequence. This means that associations between successive motor chunks may facilitate or even take over the selection and loading processes from the cognitive processor (in analogy with associative learning between individual responses in, for example, the SRT task). Empirical evidence for such associative learning on the motor chunk level was provided by Verwey and colleagues (2010) and Verwey and colleagues (2014), who demonstrated that the concatenation interval was not slowed any more by a secondary task than other key-presses. This suggests that, after extensive practice, the cognitive processor is no longer involved in the concatenation process when motor chunks are repeatedly executed in a fixed order, thereby evidencing the existence of two distinct processors instead of a single graded processing resource.
The neural basis of sequential action.

Next to cognitive models of sequence learning that try to catch the processes underlying sequential behavior, there have been several attempts to localize the neural underpinnings of sequential action. These attempts resulted in the proposition of some brain structures that would be involved in sequence skill among which the (dorsolateral) prefrontal cortex (e.g. Averbeck, Sohn, & Lee, 2006; Pascual-Leone, Wassermann, Grafman, & Hallett, 1996; Robertson & Pascual-Leone, 2003), parts of the basal ganglia such as the putamen (e.g. Wymbs, Basset, Mucha, Porter, & Grafton, 2012) and the caudate nucleus (e.g. Kermadi & Joseph, 1995), the (pre)motor cortex (e.g. Halsband and Freund, 1990; Pascual-Leone et al., 1994), and parietal regions (e.g. Grafton, Hazeltine, & Ivry, 1995). Although there is still considerable disagreement regarding the locus of specific sequence functions (i.e. what brain regions underlie which functions), there have been some efforts (e.g. Abrahamse et al., 2013) to map the abovementioned execution modes on specific regions of the brain that contribute to sequence skill.

When performing a sequence in the reaction mode, the selection of each individual response on the basis of a key-specific stimulus probably boils down to brain regions that are responsible for spatial response selection, such as the premotor (PMC), parietal (PC) and prefrontal cortex (PFC) (Jiang & Kanwisher, 2003; Schwarb & Schumacher, 2008). Furthermore, the associative striatum may provide a functional link between prefrontal and posterior cortices (i.e. associative cortico-striatal loop; Seger, 2008) to support the initial S-R translation processes that underlie the reaction mode. Indeed, activity in the associative striatum has already been demonstrated to be associated with the early stages in sequence learning and habit formation (Ashby, Turner, & Horvitz, 2010).

With practice, however, the prefrontal cortex becomes decreasingly involved since less control is needed in order to execute the responses. This causes the activity to shift from the associative cortico-striatal-loops to sensorimotor cortico-striatal loops, involving the sensorimotor striatum, the premotor and primary motor cortices. These shifts in activity are also reflected in the execution modes that develop when a sequence becomes more familiar. Indeed, the PMC seems to be critically involved in the associative mode, while (components of) the basal ganglia (e.g. striatum) have been
shown to be more important in the chunking mode. The latter has been assumed based on studies on Parkinson’s disease (e.g. Tremblay et al., 2010) that led to the conclusion that the ability to generate motor chunks is impaired when the basal ganglia are damaged. Similarly, recent studies (Wymbs et al., 2012) showed that the concatenation processes required for the fluid transitions between motor chunks are related to the putamen – again supporting the importance of the basal ganglia for the chunking mode (see also Rhodes, Bullock, Verwey, Averbeck, & Page, 2004).

**Sequence Learning in Individuals Diagnosed with Schizophrenia**

Schizophrenia has been shown to be associated with an impaired ability to develop sensitiveness to frequently occurring sequences of events within the environment (Marvel, Schwartz, Howard, & Howard, 2005). This observation has led many researchers to develop an increased interest in the performance of patients diagnosed with schizophrenia in sequence learning. While there is ample research that investigated and confirmed explicit learning deficits in schizophrenia (e.g. impaired explicit memory, Aleman et al., 1999; Gras-Vincendon et al., 1994; Lussier & Stip, 2001; Marie et al., 2001; Woonings, Appelo, Kluiter, Slooff, & van den Bosch, 2002; impaired verbal learning, Keefe & Harvey, 2012; Landro & Ueland, 2008; Shihabuddin et al., 1998), less research has explicitly focused on explicit *movement sequence* learning in individuals with schizophrenia. The few studies that did clearly found deficits in explicit sequence learning in patients diagnosed with schizophrenia. For example, Dominey and Georgieff (2008) used the SRT task in order to demonstrate that patients diagnosed with schizophrenia were able to learn the surface (implicit) structure of a sequence, whereas they failed to learn the abstract (explicit) structure. Similarly, Pedersen and colleagues (2008) observed deficits in explicit sequence learning by having participants recall the sequence immediately after the SRT.

Contrarily to explicit sequence learning, findings are less consistent with respect to impairments in implicit learning. Many recent studies report abnormal implicit sequence learning in individuals suffering from schizophrenia (Green, Kern, Williams, McGurk, & Kee, 1997; Marvel et al., 2005; Schwartz, Howard, Howard Jr., Hovaguimian, & Deutsch, 2003; Siegert et al., 2008), though there are some that demonstrate intact implicit sequence processing (Dominey & Georgieff, 1997; Reiss et
al., 2006). This discrepancy cannot be explained by methodological features since all of the aforementioned studies used the SRT task. However, it appears that it can be accounted for by the medication patients diagnosed with schizophrenia take. Indeed, the reported implicit learning deficits may be the result of the dopamine antagonist antipsychotic medication schizophrenia patients take, rather than the underlying illness itself. In this respect, some studies have found largely intact implicit learning in patients who take atypical antipsychotic medication, whereas patients taking typical antipsychotics showed impaired implicit learning (Scherer et al., 2004; Stevens et al., 2002).

In addition to these behavioral findings, a lot of structural and functional abnormalities at the brain level may help to account for schizophrenic performance in sequence learning. Despite the multitude of such abnormalities, yet very little studies evaluated sequence learning in patients diagnosed with schizophrenia at the neural level. One fMRI investigation that is worth noting at this point is a study by Kumari and colleagues (2002). In this study, six schizophrenia patients who were taking antipsychotic medication and six healthy controls were tested on a spatial sequence consisting of several items, with every fourth being determined at random. Unlike healthy controls, patients seemed to show no sequence learning in this task. Moreover, sequence learning performance in healthy controls was accompanied by increased activity in the frontal lobe, striatum, thalamus, precuneus, cerebellum and cingulate gyrus, whereas in patients diagnosed with schizophrenia only the anterior inferior gyrus was significantly activated. This study was the first to report neural activation differences between healthy controls and patients diagnosed with schizophrenia with respect to sequence learning. In line with this, Rogowska, Gruber, & Yurgelun-Todd (2004) reported a significant reduction in both ipsi- and contralateral activation for both BA4 (primary motor cortex) and BA6 (premotor and supplementary motor area) in schizophrenic patients, as compared to controls. Other studies demonstrating abnormal activations in the schizophrenic brain reported dysfunctions of the premotor area (e.g. Kodama et al., 2001), the dorsolateral prefrontal cortex (e.g. Barch et al., 2001; Callicot et al., 2003), the basal ganglia (Bracht et al., 2013), and the striatum (e.g. Reiss et al., 2006) in patients with schizophrenia.
Sequence learning in schizophrenia can also be predicted by looking at structural abnormalities in the schizophrenic brain. For instance, Zhou and colleagues (2005) found volume reductions in the whole frontal lobe and its subregions (precentral gyrus, anterior cingulate and posterior cingulate) – regions which have previously been associated with sequence learning (Averbeck, Sohn, & Lee, 2006). Other studies found volume reductions, for example, in the prefrontal cortex (James, James, Smith, & Javaloyes, 2004), the thalamus (Andreasen et al., 1994; Buchsbaum et al., 1996) and the striatum (e.g. Corson, Nopoulos, Andreasen, Heckel, & Arndt, 1999).

However, despite these behavioral and neural observations regarding sequence learning, there still remains a gap in the literature concerning the question whether and how schizophrenia affects the learning of discrete movement sequences, as well as the development of motor chunks. The present study attempts to fill in this gap.

**Present study**

The goal of the current study was to gain more insight into discrete (explicit) movement sequence learning in patients with schizophrenia. In order to do this, the present study used the DSP task, as opposed to most studies using the SRT task in order to assess implicit and explicit sequence learning in schizophrenia. To the best of our knowledge, discrete sequence learning has never been investigated before in schizophrenia patients. As such, the current study was the first to use the DSP task in order to assess movement sequence learning in patients diagnosed with schizophrenia. This is interesting as it allowed predictions to be made both with respect to discrete sequence learning and the different sequential execution modes that have been identified for healthy people. More specifically, the present study aimed at investigating whether and to what degree patients diagnosed with schizophrenia show abnormalities in (a) overall discrete sequencing performance and (b) the reaction, associative and chunking modes. To this end, we had a group of patients diagnosed with schizophrenia and a matched control group perform a version of the standard DSP task that was adjusted to better suit research involving schizophrenia patients. Participants first practiced two discrete keying sequences, after which they performed a test phase with four conditions. In the *familiar* condition, participants executed the practiced (and thus familiar) sequences, which are typically performed in the chunking mode by healthy
controls. In the *single-stimulus* condition, only the first sequence-specific stimulus was presented and participants had to complete the rest of the practiced sequence from memory. In the *mixed-familiar* condition, participants again performed the sequences they learned, but now in the majority of the sequences the order of the stimuli slightly deviated from the practiced order. This condition has previously shown to activate the associative mode in healthy controls (Verwey & Abrahamse, 2012). Finally, in the *mixed-unfamiliar* condition, participants performed new (unfamiliar) sequences (the majority of them also including a deviation from the unfamiliar fixed sequence orders), so that sequences are executed in the reaction mode. The use of this design enabled us to look at general discrete sequence learning performance in the practice phase, while the properties and modes of sequence learning could be more deeply studied in the test phase.

We expected the control group to display the typical behavior (the three execution modes, involvement of the cognitive and motor processor, etc.) that has often been observed in sequence learning research using the DSP task. The focus of the current study, however, was on the performance of patients diagnosed with schizophrenia. In line with the majority of the behavioral studies that showed schizophrenia to be associated with reduced (especially explicit) sequence learning, we expected to observe impaired discrete sequence learning in schizophrenic patients as well. This could also be expected on the basis of brain findings related to the prefrontal cortex and the striatum. Indeed, neuroimaging studies show impairments of the (dorsolateral) prefrontal cortex (e.g. Barch et al., 2011) and the striatum (Corson et al., 1999; Reiss et al., 2006) in patients diagnosed with schizophrenia. Since these areas have been shown to be involved in sequencing skill in healthy people (see above), we hypothesized that patients diagnosed with schizophrenia would show impaired sequence learning in the DSP task as well. This would supposedly be reflected in a poorer performance of patients during practice (in terms of accuracy and/or response times), relative to controls.

Moreover, we expected patients to not rely on the chunking mode when performing the practiced sequences in the familiar and single-stimulus test phases. As it has been demonstrated that schizophrenic patients show basal ganglia deficits, a structure playing an important role in the chunking mode, we expected patients to make
less use of this execution mode, relative to controls. This would presumably lead to a performance decline for patients during the familiar and single-stimulus test phases, because both phases have been previously shown to be performed in the chunking mode. More specifically, the response time of schizophrenic patients during the familiar test phase was expected to be significantly longer compared to the control group where the chunking mode would be preserved. Similarly, we assumed that patients would make more errors during the single-stimulus test phase because of the fact that their ability to use the chunking mode would be reduced. Hence, since they could not fall back on any visual stimulus (as in the familiar test phase), they were expected to have trouble completing the sequence internally which would lead to a greater error rate as compared to the healthy control group.

Finally, we could ask ourselves whether patients would be impaired in the reaction and associative modes too. This could be tentatively suggested based on dysfunctions of the premotor cortex (PMC) in patients diagnosed with schizophrenia. Since the PMC is particularly involved in controlling sequence execution by means of S-R translations, we might carefully suggest that the performance of sequences without deviants in the mixed-unfamiliar and mixed-familiar test conditions would be slowed in the patient group.

Overall, in the present study we explored, first, whether patients diagnosed with schizophrenia are impaired in general discrete sequence learning. As outlined above, the practice phase lends itself nicely to study overall sequence learning and provide an answer to this question. Second, we explored whether patients were impaired in the different sequence execution modes, predicting that patients would perform worse in the familiar and single-stimulus test phases, and, more tentatively, in the mixed-familiar and mixed-unfamiliar conditions, relative to controls.
Method

Participants

Sixteen patients diagnosed with schizophrenia (mean age = 37.1 years, range = 24-55, 13 men) were recruited in the Psychiatric Centre Sint-Amadeus in Mortsel, the Psychiatric Clinic Broeders Alexianen in Boechout and the Dr. Guislain Psychiatric Centre in Ghent. Sixteen healthy controls were recruited (mean age = 36.4 years, range = 24-56, 13 men) through various channels and matched by age, sex, and education years to the patients in the clinical group. One participant from the patient group was excluded from the analysis because of an unusually high proportion of erroneous sequences.

All of the patients were diagnosed with schizophrenia by an interdisciplinary team or the attending physician and were treated for this condition on an outpatient or semi-permanent basis in the respective institutions. Patients with any history of neurological disorders (e.g. epilepsy), other psychiatric disorders, brain damage, serious head injury, illegal drug use, alcohol abuse or addiction were excluded from the study. Users of diazepines were excluded as well, given the long-term detrimental effects of this kind of medication on cognitive functioning (Barker, Greenwood, Jackson, & Crowe, 2004). All patients were free of psychotic symptoms (hallucinations/delusions) at the moment of testing. Control subjects had no history of Axis I DSM-IV diagnoses, psychiatric medication use or any first-degree relatives with a history of mental, motoric, sensory or neurological disorders. For all participants, the Dutch version of the Adult Reading Test (DART; Schmand, Bakker, Saan, & Louman, 1991), the Edinburgh Handedness Inventory (Oldfield, 1970) and the finger-tapping test (FTT; Reitan & Wolfson, 1993) were performed. In addition, the schizophrenic patients were asked to complete the Simpson Angus Scale (SAS; Simpson & Angus, 1970), the Neurological Evaluation Scale (NES; Buchanan & Heinrichs, 1989), the Montreal Cognitive Assessment (MoCa; Nasreddine et al., 2005) and the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987).
All participants had a normal or corrected-to-normal vision and none of them were colorblind. The study protocol was approved by the Ethics Committee of the Ghent University Hospital and the local ethics committee of the involved institutions. Written informed consent was obtained from all participants prior to their enrolment in the study and participants received a monetary compensation of 35 euro upon finishing the study. Table 1 shows the demographic information of the subjects.

Table 1.

Demographic and clinical characteristics and cognitive measures of all subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Schizophrenic patients (n = 15) [mean (S.D.)]</th>
<th>Control subjects (n = 16) [mean (S.D.)]</th>
<th>Statistics</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.7 (8.8)</td>
<td>36.4 (9.0)</td>
<td>t(29) = 0.154</td>
<td>0.879</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>12/3</td>
<td>13/3</td>
<td>χ²(1) = 0.008</td>
<td>0.930</td>
</tr>
<tr>
<td>Education (in years)</td>
<td>12.5 (3.6)</td>
<td>12.6 (2.0)</td>
<td>t(29) = -0.028</td>
<td>0.978</td>
</tr>
<tr>
<td>Handedness (left/right)</td>
<td>2/13</td>
<td>2/14</td>
<td>χ²(1) = 0.005</td>
<td>0.945</td>
</tr>
<tr>
<td>PANSS total score</td>
<td>53.1 (10.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>13.1 (4.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>11.5 (3.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General psychopathology</td>
<td>28.5 (7.6)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MoCa total score</td>
<td>25.3 (2.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simpson-Angus Scale</td>
<td>2.6 (2.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological Evaluation Scale</td>
<td>7.2 (2.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory integration</td>
<td>1.5 (1.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor coordination</td>
<td>0.7 (1.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seq. of complex motor acts</td>
<td>2.1 (1.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>2.9 (1.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intellectual performance</td>
<td>98.7 (13.2)</td>
<td>104.3 (6.6)</td>
<td>t(20.29) = -1.470</td>
<td>0.157</td>
</tr>
<tr>
<td>(DART score)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fine motor skill (FTT score)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant hand (mean)</td>
<td>49.2 (8.4)</td>
<td>45.7 (7.0)</td>
<td>t(29) = 1.259</td>
<td>0.218</td>
</tr>
<tr>
<td>Non-dominant hand (mean)</td>
<td>47.9 (4.7)</td>
<td>40.4 (7.0)</td>
<td>t(29) = 3.471</td>
<td>0.002</td>
</tr>
</tbody>
</table>

a All values were computed based on the remaining sample of 15 patients.
b Education in years is calculated starting from the age of six.
Materials

Questionnaires.

*Edinburgh Handedness Inventory.* The Edinburgh Handedness Inventory (EHI) is a 12-item measurement scale used to assess the dominance of a person’s left or right hand in everyday activities (i.e. laterality). Based on participants’ answers on the items, a quantitative assessment of handedness is provided (Oldfield, 1970).

*Positive and Negative Syndrome Scale.* The Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987) is a clinical scale used for measuring positive and negative symptom severity in patients diagnosed with schizophrenia. During this 45 to 50 minutes interview the clinician assesses various subscales, among which the positive scale (7 items), the negative scale (7 items) and the general psychopathology scale (16 items). This enables the clinician to study the relationship of positive and negative symptoms to one another and to global psychopathology (Kay et al., 1987).

*Simpson-Angus Scale.* The Simpson-Angus Scale (SAS; Simpson & Angus, 1970) is a 10-item rating scale used for the assessment of neuroleptic-induced parkinsonism (NIP) in both clinical practice and research settings. Items measure gait (hypokinesia), rigidity, glabella tap, tremor and salivation. In the current study, one of the items (head dropping) was not scored due to practical reasons. As a result, overall SAS scores could range from 0 to 36.

*Neurological Evaluation Scale.* The Neurological Evaluation Scale (NES; Buchanan & Heinrichs, 1989) is a structured clinical instrument for the evaluation of neurological soft signs in schizophrenia. The battery consists of 26 items, grouped into three functional areas of interest: sensory integration, motor coordination and sequencing of complex motor acts. Abnormalities in eye movements, frontal release signs and short-term memory are not part of any subscale, though are included in the total score. Items were rated on a 3-point scale, ranging from 0 (no abnormality) to 2 (marked impairment). The present study only scored 25 out of the 26 items. Because of practical limitations, we obtained no scores for the short term memory item, neither did we record performance for the left and right hand separately.
**Montreal Cognitive Assessment.** The Montreal Cognitive Assessment (MoCa; Nasreddine et al., 2005) is a 30-item test administered in approximately ten minutes. The test assesses different cognitive domains, among which attention and concentration, memory, visuospatial abilities, executive functions, language, and orientation to time and place. This screening tool is sensitive to the presence of mild cognitive impairment (MCI) and is suited to be used in a clinical setting where assessment time is typically limited. Previous research already showed that the MoCa was sensitive enough to detect cognitive impairment in patients diagnosed with schizophrenia (Wu, Dagg, & Molgat, 2014).

**Dutch Adult Reading Test.** The Dutch version of the Adult Reading Test (DART; Schmand, Bakker, Saan, & Louman, 1991) consists of a list of fifty words with an irregular pronunciation. Administration of this test provides a good estimate of premorbid intelligence of brain damaged patients (Schmand et al., 1991). As such, the DART is particularly suited to be used with patients diagnosed with schizophrenia, due to its insensitivity to the cognitive deterioration in these patients.

**Tasks.**

**Finger-Tapping Test.** The finger-tapping test (FTT; Reitan & Wolfson, 1993) was used to examine motor functioning, more specifically, motor speed and lateralized coordination. Before administration, the participant was asked to place his or her palm flat on a manual finger-tapping device with the index finger of the hand placed on the lever. One hand at a time, the subject then had to tap the index finger on the lever as fast as possible within a 10-s interval, timed with a stop watch. The test was finished either when the counts on five consecutive trials were within five of each other or – when this requirement was not met - after ten tapping trials (Strauss, Sherman, & Spreen, 2006). The outcome measure is the mean number of taps over the trials for both the dominant and non-dominant hand. Differences in performance between both hands then reflect the brain’s functional specialization and handedness.
Discrete sequence production task.

Apparatus. Stimulus presentation, timing, and data collection were controlled using the E-Prime experimental software package (Version 2.0; Psychology Software Tools, Inc., Sharpsburg, PA). Windows services that could affect reaction times were shut down. Stimuli were presented on a 12-inch Asus display. The viewing distance was approximately 50 cm, though this was not strictly controlled. Responses were given on an azerty keyboard.

Stimuli and task. Participants were instructed to place the little, ring, middle and index fingers of their left hand on the c, v, b and n keys, respectively. Next, four black horizontally aligned square stimulus placeholders were displayed against a white background (see Figure 2). As soon as one of the placeholders was filled with green, participants had to respond to the stimulus by pressing the spatially corresponding key (e.g. n for the rightmost square). When the correct key had been pressed, the color in the square switched back to its original white background color for 50 ms\(^1\), after which the next stimulus in the sequence was presented by filling one of the other placeholders with green, and so on. Once all stimuli of the sequence were presented and (correctly) responded to, the entire screen was blanked for 1000 ms to indicate completion of the sequence. Then the black outlines were presented again for 1000 ms and the first stimulus of the next sequence appeared. Pressing a wrong key (or no key at all) resulted in an error message that was presented for 2000 ms. This unusual long period was used to motivate participants to avoid errors. The ongoing sequence was then aborted, followed by a 1000 ms lasting empty screen after which the placeholders were presented for another 1000 ms and the next sequence started.

In the practice phase, participants responded to two series of six stimuli (i.e, \(S_1\)-\(S_6\)), yielding two fixed sequences of six key presses (\(R_1\)-\(R_6\)). One of these sequences consisted of the repeated execution of the same three key presses (i.e., 2 x 3 sequence), whereas the other one involved a more complex order of six key presses (i.e., 1 x 6 sequence). Importantly, keys were rotated across sequential positions across all participants, so that each of the four fingers contributed as much to the response time at

\(^1\) The response-to-stimulus interval (RSI) of 50 ms is different from that used in the typical DSP task, in which an RSI of 0 ms is used. The increased RSI here was employed in view of the test phase, so as to allow participants to perceive an (infrequent) repetition of the same square in case of random deviants in the mixed-familiar and –unfamiliar conditions (e.g. Verwey & Abrahamse, 2012).
each sequential position. This resulted in four versions of each sequence, namely ncbncb, cvncvn, vbcvbc and bnvbnv for the 2 x 3 sequence, and nvbcbv, cbnvnbcvbn and bcvnc for the 1 x 6 sequence (see also Verwey, Lammens, & van Honk, 2002; Ruitenberg et al., 2014). The two sequences that a participant practiced never started with the same key press and their order was determined at random. Altogether, participants practiced the sequences 240 times (120 practice trials for each sequence) across six 40-trial blocks, with a 30 s break between successive blocks. During each break, participants received feedback on their mean response time and error percentage, and – in case of error rates over 8% - the additional instruction that they made too many errors and should try to improve.

After six practice blocks, participants completed a test phase. The test phase included four blocks of 32 trials, each block involving a different experimental condition separated by 30 s breaks. In each test block, each of the two sequences was presented 16 times in a random order. The order of the four test blocks was counterbalanced across participants. Three test blocks were based on the two sequences that participants already had performed during the practice blocks. In the familiar condition, participants still performed the two practiced sequences in response to the key-specific stimuli. In the single-stimulus condition, only the first sequence-specific stimulus was presented and participants had to complete the rest of the practiced sequence from memory. They were stimulated to use their gut feeling when they were not sure which key to press next. In the mixed-familiar condition, again the practiced sequences were performed, but in the majority of the sequences the order of the key-specific stimuli slightly deviated from the order that had been learned during the practice phase. More specifically, in 75% of the sequences two of the stimuli at sequential positions 2, 3, 4, 5 or 6 were randomly changed. The first key-specific stimulus always remained the same. The two changed stimuli (i.e. deviants) were not allowed to occur at consecutive positions, producing sequences with deviants at positions 2 and 4, 2 and 5, 2 and 6, 3 and 5, 3 and 6, and 4 and 6. The remaining 25% of the sequences did not include deviants and thus were identical to the sequences the participants had learned during the practice phase. Finally, in the mixed-unfamiliar condition, participants performed two novel 6-key sequences that were borrowed from the different versions of the 6-key sequences created by counterbalancing keys across
sequential positions (see above). As such, the sequences that were unfamiliar to one participant, were familiar to another participant. Similar to the mixed-familiar condition, 75% of the sequences in the mixed-unfamiliar condition also included a deviation from the unfamiliar base sequence. The interval between depressing the last key of one sequence and presenting the first key-specific stimulus of the next sequence again was set on 1000 ms in the test phase. Feedback concerning mean response time and total error percentage (per block) was provided after each test block.

![Figure 2. Depiction of a single trial (i.e., one full discrete sequence) in the DSP task. Stimulus presentation in the DSP task involved the presentation of four square stimulus placeholders that spatially corresponded to four response keys. As soon as one of the placeholders was filled with green, participants had to respond to the placeholder by pressing the corresponding key on an azerty keyboard.](image-url)
Procedure

The experiment consisted of three sessions spread out over a maximum of one week so as to avoid mental overload in patients. Upon entering the lab in the first session of the experiment, participants received information concerning the study and signed an informed consent form. They then filled out a few questionnaires. These concerned the MoCa (Nasreddine et al., 2005), the DART (Schmand et al., 1991) and the EHI (Oldfield, 1971). The first two questionnaires were administered to assess cognitive functioning in participants, the latter was carried out to determine handedness (see above). Next, participants performed the Stroop test (Stroop, 1935), as part of another – related – experiment on cognitive functioning in schizophrenia. In the second session, the FTT was administered, after which the actual experiment – the DSP task – started. Participants first completed the six practice blocks of the DSP task. They thereby received the explicit instruction that there would be two fixed 6-key sequences presented, each of them starting with another key press. After having finished the practice phase, participants completed the four blocks of the test phase. Finally, in the third and last session, participants completed the remaining scales, among which the NES (Buchanan & Heinrichs, 1989), the SAS (Simpson & Angus, 1970) and the PANSS (Kay et al., 1987). The duration of the experiment was about three and a half hours (one hour per session) for each participant.
Results

We first calculated combined mean response times (RTs) across the 2 x 3 and 1 x 6 sequences for each participant, for each block of the practice and the test phases. RT was defined as the time between stimulus presentation and depression of the correct response key. As in previous work, sequences in which one or more errors were made – thereby resulting in the instantaneous abortion of the current sequence – and the first two sequences of each (sub-)block were excluded from RT analyses (16% of the data). In addition, a sequence was omitted from the RT analyses when its mean execution time deviated more than 3 standard deviations from the mean RT across participants with in each group (patients and controls). This was done separately for the 2 x 3 and 1 x 6 sequences per (sub-)block and resulted in removal of less than 1 % of the data. A similar procedure of data removal was done for the accuracy analyses, except for the fact that erroneous sequences were not removed from these analyses. One participant in the patient group was excluded from both RT and accuracy analyses because of an unusually high proportion of error rates (more than 50% of the sequences).

Main Analysis

Practice phase.

A repeated measures ANOVA on RTs with Block (6) and Key (6) as within-subject variables and Group (2; patient versus control) as a between-subject variable showed an effect of Block, $F(2.496, 72.378) = 47.438$, $p < 0.001$, and Key, $F(2.661, 77.165) = 17.498$, $p < 0.001$, indicating that sequencing performance improved with practice and that key presses were faster past the first one. The Block x Key interaction indicated that $T_2$-$T_6$ reduced faster with practice than $T_1$, $F(8.767, 254.245) = 7.36$, $p < 0.001$. Indeed, across both groups, the $T_1$ versus $T_2$-$T_3$-$T_4$-$T_5$-$T_6$ difference increased across blocks, $t$s > -2.3, $p$s < 0.05 (except for the difference between the first and the second block, $t(30) = -0.228$, $p = 0.821$). These are all typical effects observed in DSP studies (e.g. Abrahamse et al., 2013; Ruitenberg et al., 2014; Verwey & Abrahamse, 2012). Furthermore, the presence of a Key x Group interaction, $F(2.661, 77.165) = 3.647$, $p < 0.05$, suggested that the differences between the key presses varied between both groups. Post-hoc analyses between groups revealed that – next to both patients and

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2 Throughout the analyses, degrees of freedom were adjusted using the Greenhouse-Geisser correction in cases where the assumption of sphericity was violated ($p < 0.05$).
controls being slowest on the first key press (all ts > 2.4, ps < 0.05) – controls additionally showed a drop in performance on the third key press (T₃ versus T₂-T₄, t(15) = 2.785, p < 0.05), whereas patients showed a tendency for such a drop on the fourth key press (T₄ versus T₃-T₅, t(14) = 2.000, p = 0.065). This suggests the existence of a chunking difference between patients and controls. Controls seem to show a shorter first chunk (compromising two key presses) and a longer second chunk (compromising four key presses), whereas patients display two equally long chunks (both containing three key presses). Figure 3 depicts these results.

![Figure 3](image.png)

*Figure 3.* Mean RTs per key position in the practice phase for controls and patients (over blocks). All error bars represent standard errors.

We also analyzed participants’ performance in terms of accuracy by means of a repeated measures ANOVA on proportions of correctly performed sequences with Block (6) and Key (6) as within-subject variables and Group (2) as a between-subject variable. Results showed no change in error rate across practice (p > 0.1), but there was a trend towards poorer performance in patients, relative to controls, $F(1, 29) = 3.757, p = 0.062$. Given that we expected patients to perform worse than controls, we here interpret this difference as one-tailed significant at the $\alpha = 0.10$ level. Furthermore, the Key x Group interaction, $F(3.138, 91.008) = 3.095, p < 0.05$, indicated that the patients’ error rate was higher than that of controls for some keys than for others, namely R₁, R₂ and R₄, with ts > 2.1, ps < 0.05.
In summary, the results of the practice phase showed that patients were generally not slower at executing their sequences than healthy controls. However, there was a trend for patients making more errors than controls do. Moreover, sequencing performance improved with practice in both groups, as indicated by the RT decrease across practice blocks as well as an increase in the difference between the first and subsequent key presses of a sequence with practice. Finally, analysis of the segmentation pattern suggested that patients segmented their sequences at a later point than controls did.

**Test phase.**

*Single-stimulus condition.*

For the single-stimulus condition, the variable of main interest was the number of correctly performed sequences. An independent samples t-test conducted on accuracy rates revealed a significant effect of Group, \( t(29) = 2.053, p < 0.05 \), with patients executing fewer sequences correctly, relative to controls (23% and 52%, respectively). However, a Shapiro-Wilk test indicated that the single-stimulus accuracy rates were not normally distributed in both groups, with \( W = 0.874, p < 0.001 \) for controls and \( W = 0.962, p < 0.001 \) for patients. Therefore, we conducted the same analysis again, now using the non-parametric Mann-Whitney test. This analysis again revealed a significant effect of Group, \( z = -2.169, p < 0.05 \), suggesting that patients depended more on external stimuli for the execution of familiar sequences than healthy controls.

*Familiar and unfamiliar sequences.*

RTs were first analyzed using a 3 [Condition: familiar; mixed-familiar(00); mixed-unfamiliar(00)] x 6 (Key) x 2 (Group) repeated measures ANOVA. This ANOVA included from the mixed-familiar and mixed-unfamiliar conditions only those sequences without deviants [hence the ‘(00)’]. Therefore, this analysis considers the familiar, practiced sequences without deviants, but across different Block contexts. As illustrated in Figure 4a, RTs of the mixed-familiar and mixed-unfamiliar sequences without deviating stimuli showed the typical indications for chunking (i.e., a slow R\(_1\) followed by much faster R\(_{2,6}\)) to a lesser extent than the sequences from the pure familiar block. This has been verified by the fact that the T\(_1\) to T\(_2\) reduction did not differ between mixed-familiar and mixed-unfamiliar conditions, \( t(30) = 1.891, p = 0.068 \), while for both these conditions the reduction was smaller than in the pure
familiar condition, $t > 2.9$, $p < 0.05$. Furthermore, RTs in the mixed-familiar condition were in between those of the familiar and mixed-unfamiliar conditions. This was confirmed by a Condition main effect, $F(1.512, 43.837) = 6.82$, $p < 0.05$, and a Condition x Key interaction, $F(5.347, 155.072) = 9.636$, $p < 0.001$. The observation that responses in the mixed-unfamiliar condition were slowest (551 ms), probably reflects predominantly S-R based performance in the reaction mode. Planned pairwise comparisons further confirmed that sequences without deviants in the mixed-familiar condition were executed in the associative mode (476 ms), as they were performed faster than sequences in the mixed-unfamiliar condition (551 ms; $t(30) = -7.096$, $p < 0.001$), yet slower than sequences in the familiar condition (412 ms; $t(30) = 3.488$, $p < 0.05$). These findings are align with the three sequence execution modes discussed above (see Abrahamse et al., 2013). However, as indicated by a Condition x Group interaction, $F(1.512, 43.837) = 39.014$, $p < 0.001$, this three mode-division seems to hold only for healthy controls. Indeed, pairwise comparisons confirmed that RTs in the mixed-familiar condition were in between those of the mixed-familiar and pure familiar conditions for controls only (all $t > -4$, all $p < 0.001$), while patients were showing no significant differences in RT between the familiar and mixed-familiar conditions ($t(14) = -0.641$, $p =0.532$). This suggests that patients could not rely on the chunking mode to execute familiar sequences (Figure 4b).

To further examine this claim, we subjected RTs in the familiar condition to a repeated measures ANOVA with Key (6) as within-subjects variable and Group (2) as between-subject variable. This analysis revealed a trend towards a Key x Group interaction, $F(2.679, 77.703) = 2.542$, $p = 0.069$. Follow-up comparisons showed that the longest inter-key interval for controls (i.e., $T_3$) seemed to be one-tailed significantly longer than the surrounding execution key presses (i.e., $T_2$ and $T_4$; $t(15) = 1.883$, $p = 0.079$), while this comparison (between the slowest key press, $T_4$, and the surrounding execution key presses $T_2$ and $T_3$) did not reach significance for patients, $t(14) = 1.410$, $p = 0.180$. This suggests the absence of a well-defined concatenation point in patients, thereby again confirming the observation that patients do not rely on the chunking mode to execute familiar sequences.
The earlier 3 (Condition) x 6 (Key) x 2 (Group) repeated measures ANOVA was performed on proportions of correctly performed sequences too, but showed no significant effects. Average error percentages for the controls (patients) amounted to 1.8% (2.4%), 1% (3.6%) and 2.5% (2.7%) for the familiar, mixed-familiar (no deviants) and mixed-unfamiliar (no deviants) sequences, $F(1.522, 44.145) = 1.940, p = 0.164$. These error rates do not indicate a speed-accuracy trade-off for the RT effects.
Exploratory Analyses

Motor chunk initiation in the practice phase.

We compared T1s versus T2-T6s for both patients and controls because these RTs clearly reflect partly distinct processes – as T1 is the only response time that necessarily includes full S-R translation. To do so, RTs of the first key press (T1) were averaged to compute the mean initiation RT per participant. The RTs of the remaining key presses (T2-T6) were averaged to calculate the mean execution RT, reflecting mainly execution processes. We submitted these RTs to a repeated measures ANOVA with Block (6) and Phase (2; T1 versus T2-T6) as within-subject variables and Group (2) as a between-subject variable. Results revealed a significant main effect of Block, F(2.67, 77.431) = 30.911, p < 0.001, and Phase, F(1, 29) = 34.587, p < 0.001, again indicating that sequencing performance improved with practice and that initiating motor chunks took longer than executing other key presses within the sequence (580 ms versus 478 ms). A marginally significant Phase x Group interaction indicated that patients displayed a less steep drop in RTs from initiation to execution, relative to controls, F(1, 29) = 3.694, p = 0.064. Indeed, we found a trend towards a smaller T1 to T2-T6 reduction in patients (34 ms), as compared to controls (67 ms), t(29) = 1.922, p = 0.064. Furthermore, the presence of a significant Phase x Block interaction suggested that T2-T6 reduced faster with practice than T1, which is in line with the earlier found Key x Block interaction. Taken together, these results suggest that patients were as fast as controls in sequence initiation and execution, however, they seemed to show a smaller difference between initiation and execution RTs, relative to controls.

The same repeated measures ANOVA was repeated on the proportion of correctly executed sequences. This yielded a significant main effect of Group, F(1, 29) = 4.921, p < 0.05, which again suggests that – in general – patients were significantly impaired in initiating and executing discrete movement sequences, relative to controls.
Differences between sequences.

To explore possible sequence-dependent differences in RTs and accuracies between patients and controls, below we ran the same ANOVAs as before on RTs and accuracies of the 1 x 6 and 2 x 3 sequences separately. Due to methodological coincidence, some participants (n = 1 control and n = 1 patient) did not execute non-deviant 1 x 6 sequences in the mixed-unfamiliar condition. Therefore, the analysis for the 1 x 6 sequences in the test phase was limited to n = 15 controls and n = 14 patients. Similarly, some participants (n = 1 control and n = 3 patients) did not execute non-deviant 2 x 3 sequences in the mixed-familiar condition. Hence, the analysis for the 2 x 3 sequences in the test phase was carried out on the remaining sample of n = 15 controls and n = 12 patients.

Practice phase. Individual RTs of the 1 x 6 sequence were first subjected to a repeated measures 6 (Block) x 6 (Key) x 2 (Group) design with Group as between-subjects variable. Again, sequencing performance improved with practice, \( F(3.762, 109.108) = 68.02, p < 0.00 \), and participants seemed to be faster on key presses past the first one, \( F(3.671, 106.451) = 8.934, p < 0.001 \). In addition, the Key x Group interaction, \( F(3.671, 106.451) = 4.628, p < 0.05 \), suggested the existence of key differences across groups. Planned comparisons showed that patients were significantly slower on the second and last key press, relative to controls \( (ts > -2.2, ps < 0.05) \). As illustrated by figure 5, this indicates that patients responded as quickly as controls to the first stimulus, but then needed to identify and prepare the remaining sequence, resulting in a slower second key press. Noteworthy – and contrarily to what we have found in the main analysis - we were not able to confirm the earlier found chunking points at the third and fourth key press, for controls and patients respectively \( (ts < 1.6, ps > 0.10) \). Furthermore, a significant Block x Key interaction, \( F(7.729, 224.138) = 5.599, p < 0.001 \), confirmed that key presses at some sequential locations gained more from practice than others. The same ANOVA on proportions of correctly performed 1 x 6 sequences showed no significant effects at all.
Results of the 2 x 3 sequence version of the above ANOVA once again showed that RTs significantly decreased with practice, $F(2.337, 67.761) = 39.514, p < 0.001$, and that some keys improved more than others across blocks, $F(7.763, 225.134) = 3.557, p < 0.05$. In contrast to the 1 x 6 sequence, however, we now found a more convergent pattern of key-specific RTs across groups, $F(2.61, 75.687) = 1.888, p = 0.146$ (see figure 6). Importantly, we again found the earlier defined chunking points at the third key press for controls and the fourth key press for patients ($t > 2.2, ps < 0.05$). The same ANOVA on proportions of correctly performed 2 x 3 sequences showed no significant effects at all.
Summarizing, these results suggested that the differences in the segmentation pattern between controls and patients in the practice phase were probably due to the existence of chunking differences in the 2 x 3 sequence, since the 1 x 6 sequence did not show these chunking points. However, we did find significant differences between healthy controls and patients in their RTs at the second and sixth key press when executing a 1 x 6 sequence. This indicates that the second key press for patients was kind of a chunk-initiation key press, whereas for controls it was rather an execution key press. This potentially can account for the less steep drop in RTs that was observed in patients when analyzing the difference between mean initiation and execution times.

**Test phase.**

**Single-stimulus condition.**

A more detailed analysis on the proportion of correctly performed sequences in the single-stimulus condition for the 1 x 6 and 2 x 3 sequences separately, showed that patients correctly executed less 1 x 6 sequences than controls (0.20 versus 0.53), \( t(28.112) = 2.382, p < 0.05 \). For the 2 x 3 sequence, however, there was no reliable performance difference between both groups (0.25 versus 0.50), \( t(29) = 1.614, p = 0.117 \). Again, results from the Shapiro-Wilk test indicated that the data was not normally distributed in both groups, with \( W = 0.808, p < 0.05 \) for the 1 x 6 sequence and \( W = 0.751, p < 0.001 \) for the 2 x 3 sequence for controls and \( W = 0.674, p < 0.001 \) for the 1 x 6 sequence and \( W = 0.653, p < 0.001 \) for the 2 x 3 sequence for patients. Hence, we again conducted non-parametric Mann-Whitney tests. This analysis again revealed a significant Group difference for the 1 x 6 sequence, \( z = -2.305, p < 0.05 \), but not for the 2 x 3 sequence, \( z = -1.25, p = 0.247 \). These results suggest that – for the 1 x 6 sequences only - patients were more dependent on the key-specific stimuli when producing the familiar sequences than healthy controls were. The absence of significant differences in the 2 x 3 sequence then can potentially be accounted for either by the lower degree of difficulty - and hence the decreased need for external stimuli – that are inherent to this kind of sequence, or by reduced power, since the absolute difference is similar to the 1 x 6 sequence.
Familiar and unfamiliar sequences.

Results of a repeated measures ANOVA on mean RTs of the 1 x 6 sequence with Condition [3; familiar versus mixed-familiar(00) versus mixed-unfamiliar(00)] and Key (6) as within-subject factors and Group (2; patients versus controls) as between-subject factor revealed that performance in the three test conditions differed substantially, $F(1.579, 42.634) = 28.875$, $p < 0.001$. Generally, sequences were performed faster in the familiar condition (434 ms) than in the mixed-unfamiliar (without deviants) condition (566 ms), with sequences in the mixed-familiar (without deviants) condition in between (494 ms). However, the significant Condition x Group interaction, $F(1.579, 42.634) = 7.35$, $p < 0.05$, suggests that this only holds for controls, while patients performed sequences equally fast in the familiar and mixed-unfamiliar conditions. Detailed analyses indeed revealed significant differences between all possible pairwise comparisons [familiar, mixed-familiar(00) and mixed-unfamiliar(00)] within the control group, all $ts > -3.5$, all $ps < 0.05$, but not in the patient group, where we found significant differences for all but one of the three comparisons ($ts > -3.8$, $ps < 0.05$). There was no significant difference between RTs produced in the familiar condition and those in the mixed-familiar condition, $t(13) = 0.016$, $p = 0.988$. Together with the observed trend for controls to execute sequences faster in the familiar condition than patients do ($t(27) = -1.74$, $p = 0.093$), this again confirms the earlier reported finding that patients are less likely to rely on the chunking mode to execute familiar sequences.

Results further showed that RTs differed as a function of key position in the sequence, $F(3.393, 91.617) = 5.339$, $p < 0.05$. However, a Condition x Key interaction suggested that these differences varied for the three test conditions, $F(4.173, 112.669) = 6.346$, $p < 0.001$, while a marginally significant Condition x Key x Group interaction suggested that this was further modulated by Group, $F(4.173, 112.669) = 2.14$, $p = 0.078$. As depicted in figure 6, patients and controls seem to execute familiar sequences in the same way, whereas they seem to show a significantly different pattern for the mixed-familiar and mixed-unfamiliar sequences.
RTs for the 2 x 3 sequence were subjected to the same repeated measures ANOVA with Condition (3), Key (6) and Group (2) as relevant factors. In addition to the effects of Condition and Condition x Group found in the above analyses, results here showed a slightly different response pattern across key positions, as well as a distinguishable Condition x Key interaction. Here, no Condition x Key x Group interaction was found.

Proportions of correctly performed sequences of the 1 x 6 and 2 x 3 sequences in the test phase were also analyzed by using two separate repeated measures ANOVAs including the same variables as outlined above. For the 1 x 6 sequence, this only revealed a trend towards a Condition main effect, $F(1.768, 47.742) = 2.764, p = 0.072$. For the 2 x 3 sequence, the analysis did not show any significant main or interaction effects.

Taken together, findings of the exploratory RT and accuracy analyses looking at the 1 x 6 and 2 x 3 sequences separately converge with those of the overall analyses for the test phase in that the three of them showed no RT differences between the familiar and mixed-familiar conditions in patients. This suggests that patients could – for some reason - not rely on the chunking mode to execute familiar sequences.
Discrete Sequence Learning, Symptoms and Cognitive and Motoric functioning

Only accuracy but not speed of sequence execution was significantly poorer for schizophrenic patients than for control patients in both the practice and single-stimulus test phases. Moreover, patients but not controls showed no RT differences between the familiar and mixed-familiar (without deviants) test conditions. To rule out the possibility that these findings reflect more subtle disturbances in extrapyramidal or neurologic functions, we computed one-tailed Spearman correlations between patients’ behavioral performance and their score on the SAS and NES (sub-)scales. For both error rates in the practice and single-stimulus phases, as well as for the RT difference between the familiar and mixed-familiar conditions, this revealed no significant correlations ($p_s > 0.09, p_s > 0.13, p_s > 0.16$, respectively), indicating that differences in behavioral performance between patients and controls could not been driven by patients’ extrapyramidal or neurological symptoms. The same can be concluded based on patients’ performance on the finger tapping task: since patients in our study seem to be even better than controls when it comes to fine motor functioning, the observed effects cannot be accounted for by patients’ motoric abnormalities as both findings go in opposite directions.

Secondly, our results cannot be explained by intellectual differences between both groups. More specifically, patients and controls did not differ in terms of premorbid intellectual performance, $t(20.29) = -1.47, p = 0.157$, neither did they show a mean MoCa score that was far below the clinical cut-off of 26 ($M = 25.3; SD = 2.5$). These findings indicate that patients would certainly have been able to comprehend the instructions, thereby excluding the possibility that behavioral differences between groups could be attributed to intellectual differences at the group level.

Finally, there were no significant correlations between discrete sequence learning (as indicated by patients’ accuracy in the practice and single stimulus phases on one hand and the RT difference between the familiar and mixed-familiar conditions on the other hand) and either the PANSS total score or sub-scores in the group of schizophrenic patients. This suggests that the degree of sequence learning in patients diagnosed with schizophrenia was independent of the severity of their symptoms.
Discussion

The present study examined whether and to what extent patients diagnosed with schizophrenia show abnormalities in skilled execution of motor sequences. More specifically, it examined whether patients would be generally impaired (i.e., being slower and/or having higher error rates relative to healthy controls) when executing sequences in the practice phase. Furthermore, it investigated whether patients – like healthy controls – switch in the test phase from responding to key specific stimuli in the reaction mode to executing the sequence without much external guidance in the chunking mode, with an intermediate associative mode in between. As to the hypotheses in the introduction, it can be concluded, first, that the present study provides evidence for impaired overall discrete sequence learning in patients. Second, the hypothesis that patients diagnosed with schizophrenia would display deficits related to the chunking mode was confirmed, and, it appeared that patients as a group continued to require external guidance for sequence execution. Finally, the present study was not able to support the notion that patients would show an impaired use of the reaction and associative modes in the test phase. Below, we will subsequently elaborate on each of these points.

Impaired Discrete Sequence Learning in Schizophrenia

The current results revealed that patients performed significantly worse than controls when initiating and executing sequences in the practice phase. However, this effect seems to be dependent on the behavioral measure that was considered. In terms of response time, performance did not differ and improved to a similar degree in patients and controls, but in terms of accuracy, patients displayed error rates that were significantly larger than those of controls. These findings can be explained by the idea that patients differ from healthy controls in terms of their capacity to learn motor skills, but not in terms of cognitive speed. This observation is in line with the study of Pedersen and colleagues (2008) who showed impaired explicit sequence learning in schizophrenic patients with respect to error rates, though not when considering response times. At a more general level, our results also fit well with several reports (e.g. Kodama et al., 2001; Schwartz, Rosse, Veazey, & Deutsch, 1996) showing overall impairments in motor skill learning in schizophrenic patients.
Although the nature of the deficit behind the failure of discrete sequence learning in schizophrenia still remains to be explored, we tentatively suggest it – in line with our hypothesis – to be related to frontostriatal deficits. This suggestion seems to be in line with the proposal of several investigators that frontostriatal dysfunction leads to a variety of symptoms in schizophrenia, such as positive and negative symptoms of the disease, as well as disorders of motor programming, eye movements and directed attention (Early, Posner, Reiman, & Raichle, 1989; Frith and Done, 1988; Gray, Feldon, Rawlins, Hemsley, & Smith, 1991). Nevertheless, the current study only allows speculating about the underlying neurophysiology of impaired sequencing performance, and we believe that further research of patients diagnosed with schizophrenia is required to fully understand the precise relationship between frontostriatal abnormalities and discrete sequence learning.

Importantly, when interpreting the present data, several limitations should be taken into account. First, deficits in sequence learning could reflect an underlying neurological or motor problem that impaired patients in learning or executing the structure of the motor sequences. However, in our patient sample, accuracies in the practice phase did not correlate significantly with either the mean NES (sub-)score(s) or mean SAS score, indicating that our results cannot be driven by neurological or motor deficits in the patient group. This was further confirmed by their higher FTT scores, relative to controls. Second, poorer performance in schizophrenic patients is often argued to reflect a lack of motivation. Nevertheless, the relatively high level of response speed in the DSP task and the overall good performance in the administered cognitive and motor tests (i.e., DART, MoCa, FTT) do not support this interpretation. Third, motor symptoms have already been reported to co-vary with negative symptoms (Walther & Strik, 2012). However, in our study there were no significant correlations between execution accuracy in the practice phase and PANSS total scores or sub-scores. That is, discrete sequence learning performance was independent of the severity of schizophrenic symptoms. These findings indicate that the observed sequence learning deficits were specific to the pathology of the patients, rather than being driven by other peripheral factors.
Patients Obtain Only Two Modes of Sequence Execution

As expected, we observed that patients as a group had not switched to the chunking mode when executing familiar sequences in the test phase, whereas healthy controls had. This indicates a strategic difference between both groups. Two observations seem to confirm this hypothesis. First of all, the current results showed that for both the overall analysis and the analysis for the 1 x 6 sequence separately, schizophrenic patients made significantly more errors in the single-stimulus condition than controls did. This suggests that patients depend more on external stimuli – i.e., on the direct one-by-one S-R translation processes of the cognitive processor – when executing familiar sequences, while healthy controls could enhance performance in the single-stimulus condition through relying on their motor chunks. Secondly – although patients were not significantly slower in executing familiar sequences than controls were – patients did not show performance differences between the pure-familiar and mixed-familiar conditions, while in controls sequencing performance was faster in the familiar than in the mixed-familiar condition. In line with the DPM, the absence of such a response time difference in patients might indicate that they did not use the chunking mode to execute familiar sequences, and instead remained largely dependent on external stimuli when performing sequences. This is further corroborated by the observation that patients did not display a well-defined chunking point in the familiar test condition, whereas controls did.

Since schizophrenic patients typically show deviant motor and neurological functioning, we again cannot completely rule out the possibility that our findings regarding the chunking mode reflect more subtle motor and neurological deficiencies rather than chunking mode deficits. Nonetheless, patients’ accuracies in the single-stimulus condition as well as their RT difference between the familiar and mixed-familiar conditions were not significantly correlated with either mean SAS or mean NES (sub-)scores. Similarly, there were no significant correlations between both behavioral performance measures and PANSS ratings, thereby again confirming the pathology-specificity of our findings.
An explanation that is worth considering to account for the observed absence of a chunking mode in patients is related to differences in working memory capacity between patients and controls (see also Schwartz et al., 2003). As already demonstrated, patients diagnosed with schizophrenia often experience severe working memory capacity problems (e.g. Goldman-Rakic, 1994; Jansma, Ramsey, van der Wee, & Kahn, 2003). With respect to the single-stimulus condition, this can explain why patients showed higher error rates in completing the sequences than controls did. Indeed, since executing sequences in the single-stimulus condition necessarily implies the reliance on participants’ working memory to execute keys 2-6, participants with working memory deficits will be substantially impaired in sequence completion. Similarly, we expect the absence of performance differences in the familiar and mixed-familiar test phases in the patient group to be driven by working memory too. As indicated by Abrahamse and colleagues (2013), sequence execution in the chunking mode is largely dependent on the loading of movement series into a motor buffer that is frequently been thought of as part of our working memory (Henry & Rogers, 1960; Smyth & Pendleton, 1989; Verwey, 1999). Hence, we can suggest that schizophrenic patients – due to their memory deficits – would not have been able to translate sequences into a single motor chunk and load it into the motor buffer (i.e., chunking) because the capacity of their motor buffer would simply not allow to store these motor chunks. This can explain why patients did not respond faster to sequences in the familiar condition than in the mixed-familiar condition, and instead remained largely dependent on the guidance by external stimuli. Future research into the relationship between chunking deficits and impaired memory capacity in schizophrenia is needed to further substantiate this hypothesis.

Next to the chunking mode being impaired in patients, we also tentatively suggested patients’ sequence execution time to be larger than that of controls in the reaction and associative modes – based on the presumed role of the PMC in S-R based sequencing performance. However, the current results showed no effect of group on sequence execution in the mixed-familiar and mixed-unfamiliar ([00] sequences) conditions, and thus did not support our hypothesis that patients would be impaired on the associative and reaction modes too. The same conclusion follows from the observation that patients’ sequence execution was faster in the mixed-familiar than in the mixed-unfamiliar condition. In line with the DPM, this performance difference
confirms that patients were able to develop associations between successive responses with practice (i.e., associative mode), so that performance in the mixed-familiar condition was better than in the mixed-unfamiliar condition – where completely new sequences were executed in the reaction mode. Theoretically, two potential explanations are worth considering for the intactness of the reaction and associative modes. First, we can explain these findings by re-interpreting the existing literature regarding the abnormal activation pattern of the premotor cortex in schizophrenia. As Marvel and colleagues (2007) already demonstrated, abnormal PMC activities in patients performing a sequence learning task were associated with the use of an external stimulus-driven visuospatial strategy to process sequential stimuli. This learning strategy lends itself perfectly to be used in both the reaction and associative modes, since sequence execution in these modes is largely or even entirely based on the guidance by external stimuli. Therefore, the presumed PMC abnormalities in the schizophrenic brain should be taken as evidence for a better rather than an impaired use of the reaction and associative modes – contrarily to what we expected in the introduction.

Alternatively, Wymbs and Grafton (2013) recently demonstrated that the PMC is mainly active during the execution of moderately practiced sequences. The present study did not involve such sequences, since patients executed either completely new sequences in the mixed-familiar (with deviants) and mixed-unfamiliar conditions, or well-practiced movement sequences in the mixed-familiar (without deviants), familiar and single-stimulus conditions. Hence, participants did not perform sequences that were only moderately practiced. This might explain why we did not observe the hypothesized impaired use of the reaction and associative modes in patients.

**Do Patients Chunk in the Practice Phase?**

Even though we did not obtain evidence that patients used the chunking mode to execute sequences during the test phase, our results showed indications that patients chunked when practicing sequences. Indeed, we observed a significantly slower response around halfway through the sequence (i.e., concatenation point) for both controls and patients, in the practice phase. According to the DSP literature (e.g. Abrahamse et al., 2013; Verwey & Eikelboom, 2003; Verwey et al., 2010), this concatenation point indexes the transition from one motor chunk to another, hence
indicating the usage of the chunking mode. However, this seems to be incompatible with the observation that patients do not chunk when executing sequences in the test phase. One may argue that this finding could be tentatively explained by the formation of cognitive chunks, rather than motor chunks. Indeed, as outlined before, response times were expressed by the time between stimulus presentation and depression of the correct key. As such, they reflect the time that is needed to select the correct button based on memory – thereby leaving room for the contribution of cognitive components (e.g. Sakai et al., 2003). It is possible that patients cognitively segmented their sequences to reduce the working memory load, and that this process of cognitive chunking led to the formation of a motor chunking-alike concatenation point. More specifically, imagine that patients have the tendency to group the representations of a couple of key presses together in some discrete cognitive chunks (e.g. the phone number 1324471 chunked into 1324-471). It can be expected that within a chunk (i.e., 1324 and 471), everything proceeds smoothly and automatically, whereas the transition to the next cognitive chunk (i.e., 471 after 1324) results in a temporal incoherence since the second chunk is not necessarily predictable from the first one. Hence, it is possible that the lengthened response time for patients at the fourth key press in the practice phase reflects the cognitive chunking of key presses, rather than the use of the motor chunking mode – suggesting that both chunking modes can show up independently of each other (see also Pike & Carter, 2010). This hypothesis of independency is in line with the notion that the cognitive and motor processor of the DPM are two distinct processors, rather than a single graded processing resource (Abrahamsen et al., 2013). Still, future research is needed to further support this hypothesis.

**Methodological Limitations of the Study**

The current study has certain methodological limitations. One of the limits is the small size of our samples. Nonetheless, the statistical power was still sufficient to detect differences between schizophrenic patients and normal controls. Another drawback concerns the somewhat limited number of trials of which the DSP task consisted. Usually, sequences in the DSP task are repeated approximately 500-1000 times in the practice phase. In our study, each sequence was executed not more than 120 times before participants went on to the test phase. This was done to make sure that the patients were not over-tested, since a fatigue effect could have resulted in the failure to
perform the DSP task accurately – hence devaluing our findings. Finally, all patients in our study were on antipsychotic medication. Since antipsychotics might be expected to interfere with visuomotor learning (e.g. Weniger & Irle, 2008), our findings could be the result of the properties of the antipsychotic drugs patients take rather than being a feature of the disease. Nevertheless, all subjects received atypical antipsychotics (with two patients receiving the mixed combination of typical and atypical antipsychotics) which have been shown to have rather favorable effects on cognitive and motor functions (Keefe et al., 2004; Meltzer & McGurk, 1999). As such, we could tentatively suggest that our results are an underestimation of the real effects that exist in our patient population. Future research concerning the potential role of antipsychotic medications in performance on the discrete sequence learning tasks is needed to further support this hypothesis.

**Practical Implications**

To summarize thus far, despite the abovementioned drawbacks, it may be concluded that the present study shows indications for impaired discrete sequence learning in schizophrenic patients, and, more specifically, for the absence of motor chunks in patients. The challenge here is how to relate these two major conclusions to our existing knowledge and understanding of the disorder itself. It is of course interesting to know that people diagnosed with schizophrenia may demonstrate less discrete sequence learning than healthy controls, but what possible relevance does this have for understanding and treating schizophrenia? We can only speculate about the answer to this question, but an article by Morrens and colleagues (2007) offers an idea. As argued by these authors, psychomotor activities – both discrete and continuous – are a key element in determining functional outcome in schizophrenia. Indeed, psychomotor activities express our knowledge and capabilities, but they are also essential even in our most straightforward daily care activities, e.g. dressing, cleaning and cooking. Hence, getting more insight into these activities, and, more specifically, into discrete sequence learning, can be a stepping stone in improving patients’ abilities to perform daily functions – thereby reducing the care burden for family members.
Conclusion

In conclusion, the present data provide evidence for discrete sequence learning deficits – which are not a side-effect of neurological or extrapyramidal conditions – in patients diagnosed with schizophrenia. In particular, schizophrenic patients seem to have a limited capacity to learn motor skills because they – in addition to higher error rates – continue executing movement sequences as series of individual movements, rather than that they execute familiar movement sequences as an integrated movement pattern. As a consequence, we argue that in patients, the cognitive processor seems to remain dominant in the execution of movement sequences, while for healthy controls practice leads to motor chunking that is dominated by an independent motor processor. In all, the present findings are in line with the notion that (a) sequence learning is often impaired in schizophrenia and (b) there are several modes that underlie the execution of movement sequences, of which the relative contribution differs between patients diagnosed with schizophrenia and healthy controls. Pharmacological and rehabilitation interventions should aim at improving the functioning of these processes, which are associated with several functional outcomes in schizophrenia.
Cognitieve stoornissen in schizofrenie worden dikwijls gekenmerkt door afwijkingen in motorisch functioneren, waaronder problemen met sensorische integratie, motorische coördinatiestoornissen en verstoringen in het uitvoeren van complexe motorische sequenties vallen. Hoewel veel studies zich de voorbije jaren gefocust hebben op het leren van continue motorische sequenties op zowel impliciet en expliciet niveau, heeft geen enkele studie zich reeds toegelegd op het bestuderen van discreet sequentieleren (i.e., het leren van korte en goed afgebakende acties die een duidelijk begin en einde kennen) in schizofrenie. In de huidige studie hebben we deze leemte weggewerkt door een variant van de discrete sequence production (DSP) taak te gebruiken. In de oefenfase dienden patiënten en controles te reageren op twee discrete sequenties bestaande uit 6 toets-corresponderende stimuli – teneinde vertrouwd te raken met deze sequenties. In de daaropvolgende test fase voerden ze deze twee sequenties vervolgens uit onder verschillende testcondities, en leerden ze ook twee nieuwe sequenties. Onze resultaten suggereren dat schizofrenen problemen ondervinden in het leren van discrete motorische sequenties. Bovendien vonden we dat schizofrene patiënten niet in staat waren om motor chunks te gebruiken wanneer ze sequenties uitvoerden, en in plaats daarvan afhankelijk bleven van externe stimuli voor het uitvoeren van motorische sequenties. De huidige studie is de eerste om aan te tonen dat schizofrenen – naast het ondervinden van problemen in het leren van (continue) impliciete en expliciete sequenties – ook beperkt zijn in het verwerven van discrete motorische vaardigheden. Implicaties van onze resultaten voor functionele beperkingen gerelateerd aan schizofrenie werden kort besproken.
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