Faculty of Medicine and Health Sciences

Hitting the target

Motor Learning and Performance in Schizophrenia and Ageing

Het doel raken
Motorisch leervermogen en prestatie
bij schizofrenie en veroudering

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CHAPTER I - INTRODUCTION

GENERAL BACKGROUND

Motor symptoms in schizophrenia

Schizophrenia is a severe mental disorder with a worldwide prevalence of 0.3-1%[1]. It is characterized by multiple symptom clusters, including psychotic or *positive symptoms* (such as delusions, hallucinations, formal thought disorders and disorganized behavior), more persistent *negative symptoms* (such as a diminished facial expression, emotions, speech and/or social interest) and *mood symptoms* (such as depression). Additionally, patients with schizophrenia often exhibit a *cognitive decline* and *motor symptoms*.[2]

Cognitive symptoms, dating back to their initial description in the late 1800s when schizophrenia was initially termed *'dementia praecox*,' signifying premature dementia, have consistently stood as a defining characteristic of this disorder. They include impairments in working memory, attention, executive functioning (planning, organizing, and decision making), reasoning, abstract thinking, problem solving, processing speed, visual and verbal learning.[3] These symptoms are most closely related to problems with daily functioning as they can make it hard for people with schizophrenia to live independently in society.

Schizophrenia is also characterized by various *motor symptom clusters*[4], including neurological soft signs (subtle deficits in sensory integration, motor coordination, and sequencing of complex motor acts), abnormal involuntary movements (such as dyskinesias), psychomotor slowing (reduced movement speed in planning, initiation and execution of fine motor tasks), catatonia (such as immobility/stupor, mutism, catalepsy, grimacing, echopraxia, stereotypy, mannerisms) and extrapyramidal symptoms (EPS, such as Parkinsonism, akathisia, acute dystonic reactions and tardive dyskinesia).[5–7] Some clusters, such as psychomotor poverty and neurological soft signs, seem to co-exist independently from each other[8].

Like the cognitive symptoms, motor abnormalities in schizophrenia were already described in the pre-neuroleptic era by Kraepelin.[5] The focus changed in the 1950s towards the positive symptoms which gave rise to the development of antipsychotics. Antipsychotics are often prescribed for the treatment of positive symptoms but may worsen EPS[5]. However, EPS seem

to be intrinsic to the illness as the frequency of motor symptoms in patients with schizophrenia who never took antipsychotics is estimated to be around 50-65% (compared to 5% in healthy controls).[9,10,11] Until today, there is no effective targeted treatment available for the motor symptoms.

The *clinical importance of motor symptoms* in schizophrenia is twofold. Firstly, they may serve as *prodromal warning signs*, as retrospective studies suggest that they often precede a first psychosis and delayed psychomotor development in young age is a known risk factor for later occurrence of psychosis.[5,12] Secondly, motor symptoms could predict the *prognosis* of the illness as they have been linked to daily functioning, psychological wellbeing, quality of life, and the clinical course and recovery of schizophrenia.[13–17] For instance, a reduced working pace has been identified as a causative factor leading to the termination of employment for some patients. Motor symptoms have been correlated with worse cognitive[5,18,19] and positive symptoms[20]. Moreover, patients with motor symptoms tend to experience more side-effects of antipsychotics and long-term follow-up studies suggest a relationship between neurological soft signs and more negative symptoms in schizophrenia.[5] These arguments prompt research into the question whether inadequate motor functioning can be ameliorated by targeted medication or training interventions.

A second reason for the study of motor learning in schizophrenia is that it can provide *insight into the complex pathophysiology* of the disorder as motor symptoms can be measured more objectively than some positive or negative symptoms.[14] Motor learning is a well explored area in neurophysiology and neuroscience for many years. Much is known, for example, about the neural basis of the two major long-standing learning paradigms i.e., sequence learning and adaptation.[21] As in the cognitive domain, separate abnormalities have been detected within the motor (learning) cluster. For example, there has been made a clear distinction between aberrances in movement planning, action planning and psychomotor speed in psychomotor slowing[22]. Some motor dysfunctions seem to be specific for schizophrenia as a study of 304 patients showed that a combination of three different motor tests made it possible to clearly distinguish between schizophrenia and other psychotic disorders.[23] In a recent review of neuroscientific studies examining sensorimotor behavior in schizophrenia, Hirjak[24] emphasized the involvement of prefrontal and

orbital brain regions, as well as (pre- and supplementary) motor areas, basal ganglia, midbrain, and cerebellum in the pathophysiology of schizophrenia. While these studies presented a mixed picture, they suggested 'the presence of dysfunction within the cerebello-thalamo-cortico-cerebellar (CTCC) network as a contributing factor to abnormal sensorimotor behavior in schizophrenia'. Similarly, it has been proposed that 'the basal ganglia and cortico-motor circuits play also a role in psychosis'[25–27] and that 'cerebellar-thalamic circuits are of crucial importance in the pathophysiology of schizophrenia'[25]. Northoff et al.[28] emphasized the significance of affective and cognitive processes associated with psychomotor symptoms, highlighting the "psycho" aspect of psychomotor symptoms, rather than just the motor component. In this context, they proposed various psychomotor mechanisms and the biochemical modulation underlying them. However, their viewpoint received criticism for not including CTCC circuits[29], leading to the subsequent inclusion of the CTCC circuit as another important psychomotor target underlying psychomotor symptoms in schizophrenia[30]. Nevertheless, the dominant mechanism or circuit responsible for these symptoms in schizophrenia remains unclear. Motor learning in schizophrenia also needs to be investigated as learning deficits have repeatedly been demonstrated in schizophrenia in the cognitive domain but less in the motor domain. Verbal and visual learning are included in the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia)-NIHM consensus cognitive battery[3,31,32]. In general, motor symptoms, and psychomotor slowing in particular[33] are, despite their clinical importance, still poorly understood in schizophrenia[34]. Luckily, there has been a renewed focus on the study of motor functioning in this disorder.[3,7,15,16,27,35] In 2019, motor learning research has gained worldwide recognition with the addition of the *'sensorimotor systems domain'* to the RDoC (Research Domain Criteria) framework of the NIMH (National Institute of Mental Health)[12]. This domain encompasses various constructs, including 'motor actions,' which involves action planning and different sensorimotor dynamics. It also encompasses the modulation and refinement of actions during development and learning. This doctoral thesis not only investigated psychomotor slowing but also extended its focus to assess the learning of various motor paradigms, aligning with the goals of the RDoC initiative.

Background on motor learning

Learning is the process of acquiring new knowledge, skills, behaviors, values, or attitudes through experience, study, or education. It is also characterized by a progressive improvement and by a retention of what was learned before. Learning can be intentional or unintentional, and can occur through various mechanisms such as observation, repetition, feedback, or reflection. It arises from the complex interaction between many different brain regions and circuits. Two types of learning are generally distinguished: declarative and procedural learning.

Declarative learning - During declarative learning one is conscious of what has been learned. The acquired knowledge can be *explicitly* stated or 'declared'. It involves learning facts, the meaning of words (i.e., semantic memory), personal memories (i.e., episodic memory) and other types of information that can be put into words. Declarative learning can occur through a variety of methods, such as reading, listening, watching, or experiencing something firsthand. The process of declarative learning typically involves encoding information into memory, storing that information, and then retrieving it when needed. In declarative learning, the 'higher' cognitive regions, such as the prefrontal cortex, and medial temporal lobe (such as the hippocampus), play an important role. This form of learning is examined by neuropsychologic test such as a word memory task such as the 'California Verbal Learning Test' (CVLT). Next to verbal memory tasks other conscious processes can be studied too, such as spatial tasks where the active motor reproduction of spatial figures or sequences has been studied (e.g., an explicit pattern learning task, EPLT). Both declarative learning tasks are studied in this doctoral thesis.

Procedural learning - Where declarative learning relates to knowing 'what' has been learned, procedural learning relates to knowing 'how' something has been learned. Procedural learning refers to the *implicit* (unconscious, unintentional) acquisition of skills, habits and behavior through repeated practice. This type of learning occurs continuously and automatically. The implicit skills are difficultly explained verbally but are demonstrated by a gradual improvement without being aware of it. Examples include mainly *motor skills* such as riding a bike, writing or tying laces, but also more cognitive skills such reading. It can occur through a variety of methods, but

it typically involves feedback, either from the environment or from an instructor. Procedural learning often works in tandem with declarative learning. The acquisition of procedural knowledge by repetition can result in declarative knowledge of a task. Vice versa, declarative knowledge may help accelerate procedural knowledge[36]. Brain regions and circuits involved in motor learning (Figure 1) are the primary motor cortex (involved in evoking localized movements in different body parts), premotor cortex (associated with the planning, initiation, anticipation of specific movements), (pre)supplementary motor cortex, the cingulate cortex (a necessary interface between cognition and motor control), the inferior parietal cortex, the basal ganglia (involved in motor control, habit formation, and reinforcement learning; as people repeat an action, the basal ganglia gradually build up a representation of that action and make it easier and more automatic to perform), hippocampus (associated mainly with declarative learning but it is also involved in procedural learning; the more explicit components are needed, the more the hippocampi are activated), thalamus, and cerebellum (involved in various roles of voluntary movement control, equilibrium, coordination, adaptation but also higher-order functions).[5] Abnormalities in these brain structures are found in schizophrenia and in ageing.

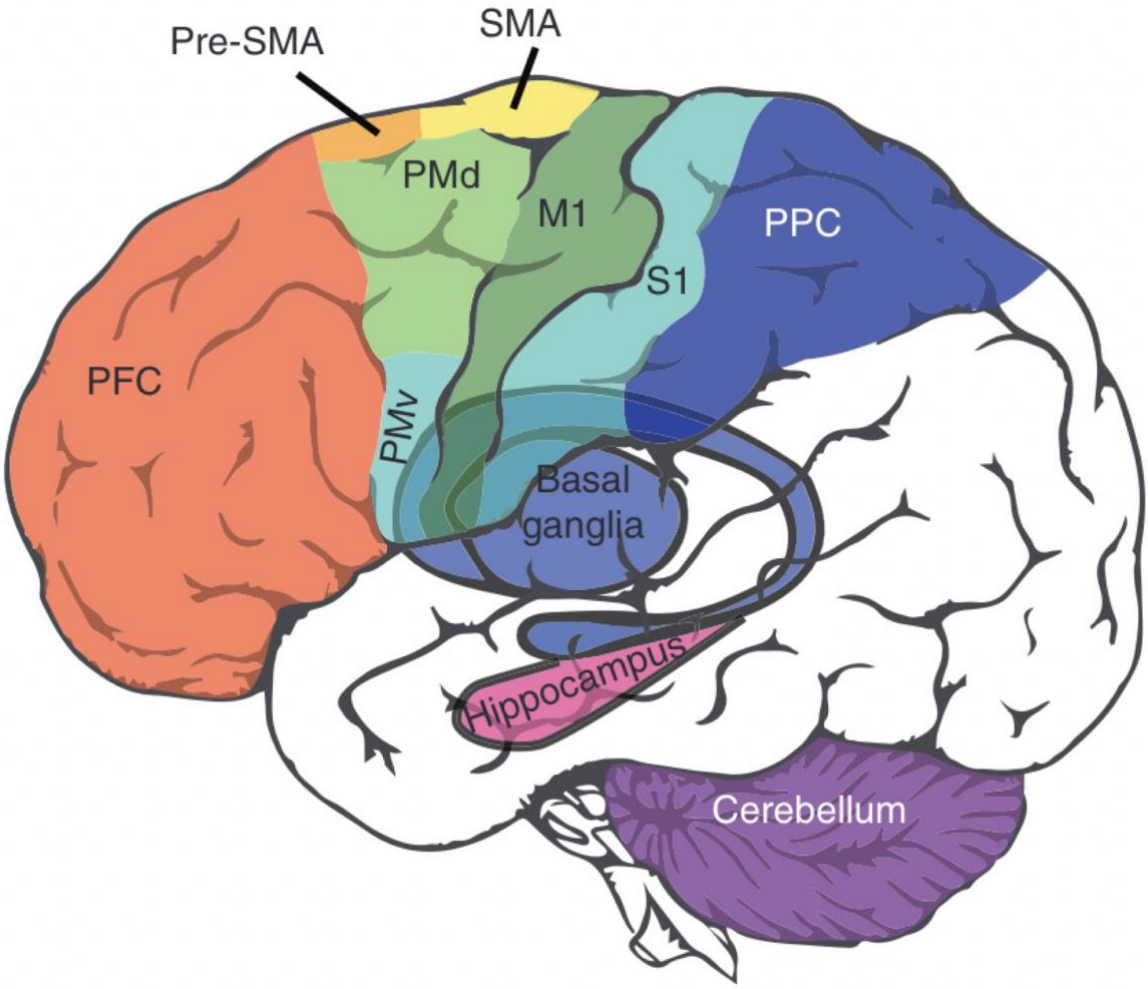

Figure 1. The involvement of various brain regions in motor learning. Abbreviations include PFC (prefrontal cortex), SMA (supplementary motor area), pre-SMA (presupplementary motor area), PMd (dorsal premotor cortex), PMv (ventral premotor cortex), M1 (primary motor cortex), S1 (primary somatosensory cortex), PPC (posterior parietal cortex), hippocampus, cerebellum, and basal ganglia. Source: Motor learning. Krakauer 2019[37].

Motor learning tasks - In the standard taxonomy for procedural learning, motor learning has a prominent place.[38] Motor learning is examined by neuropsychological tasks where new skills are learned. For example, one is taught to follow a moving target along a predictable path or along an arbitrary visuospatial sequence.

Motor learning involves numerous components. A proficient motor action, such as a tennis serve, preparing a cup of tea, or writing a digit, comprises a structured sequence of movements. Each movement within this sequence

must be executed with increasing precision, necessitating the optimization of timing, force, and trajectory. Often, these actions must be adapted to moving objects and adjusted to changing environmental conditions.

In motor learning research, these various aspects are typically studied in distinct paradigms. Recently, researchers have proposed six categories of motor learning tasks[39]: 'sequence learning', 'adaptation', 'tracking', 'precision and motor speed improvement', 'coordination', and 'applied tasks' (refer to Table 1).

Despite the shared underlying processes in these tasks, which encompass 'goal selection', 'action selection', and 'action execution' along the motor planning pathway, different task paradigms are associated with distinct brain regions. For example, sequence learning is connected to the supplementary motor area (SMA) and presupplementary motor area (pre-SMA), while adaptation predominantly relies on cerebellar activity for predictive mechanisms.[47]

Table 1. Definition of motor learning task categories after Ranganathan et al. 2021.

Task categories	**Motor learning processes involved**
Sequence	Production of a sequence of several movement responses
Adaptation	Responding to perturbations of typically well-learned movements
Tracking	Production of a desired spatiotemporal pattern that is 'time varying'
Motor speed and acuity	Production of a 'steady state' task performance level over time or trials
Coordination	Production of spatiotemporal pattern involving more than a single degree of freedom (limbs, joints, muscles)
Applied	Production of movement responses in 'real-world' situations that may involve a combination of processes

AIMS

Motor symptoms are prominent features of schizophrenia and are crucial predictors of the functional outcome[17] as they affect the proper execution of many everyday motor skills. Due to their clinical importance, further investigation into the precise underlying mechanisms of these symptoms is warranted.

The first objective of this thesis was to *measure and compare specific domains of motor learning and performance in schizophrenia*. While research on motor learning in schizophrenia is yet rather limited, motor learning as investigated by a great variety of experimental tasks, is a well-explored area in neurophysiology and neuroscience. For instance, much is known about the neural basis of *motor sequence learning* and *motor adaptation*[37,40–42]. These two learning paradigms involve different brain mechanisms and learning deficits in one task were not found to correlate with deficits in the other task in healthy individuals[38]. We included these well-studied tasks in our large test battery.

The second objective of this thesis was to *compare implicit with explicit processes* in motor learning and performance. This comes from the fact that learning deficits in schizophrenia have repeatedly been found in the cognitive domains in the past twenty years as verbal and visual learning have already been included in the MATRICS-NIHM consensus cognitive battery in 2004.[32] The literature on implicit learning in schizophrenia is smaller[43] and the results of these studies show more variability, ranging from moderate impairment[44–46] to 'intact' or 'comparable' to controls[47,48]. In these studies, a variety of tasks were used and no proper testing of the role of emerging awareness during (e.g., implicit sequence) learning was done. Moreover, explicit (or declarative/cognitive) processes seem to play a role in sequence learning and adaptation[21,49], which makes it plausible that cognitive learning deficits might also hinder patients with schizophrenia in their motor skill learning. Therefore, we separately assessed the role of explicit (cognitive) knowledge in the implicit motor learning tasks, for instance by adding explicit instructions[37,50]. Additionally, we compared performance on these implicit motor tasks with performance on explicit motor task variants and added a verbal learning task.

Third, this thesis investigated the similarities and differences in motor and cognitive functioning between schizophrenia and normal ageing. This comparison was made to determine if schizophrenia can be conceptualized as *a syndrome of accelerated ageing* ('dementia praecox') or neurodegeneration. On a clinical level, both patients with schizophrenia and and elderly individuals show a decline in motor and cognitive functioning. Recent research supports the theory that schizophrenia might be a neurodegenerative disorder with genetic, functional-organic, and neuroanatomical features of accelerated ageing,[51,52] sharing similarities with elderly individuals. Despite a wealth of literature on explicit learning deficits in senescence, the status of implicit motor learning remains quite unclear, like in schizophrenia[53–55]. In general, overall motor learning abilities tend to be maintained in old age, while there is a decline in the ability to learn fine motor tasks and acquire more complex motor tasks.[56] Sensorimotor adaptation is found to occur at a slower rate in the elderly[57–60]. Although the comparison is difficult to make, we aimed to provide a comparative image of the severity of sensorimotor decrease in schizophrenia and normal aging. If the pattern of decline in sensorimotor learning was found to be similar in both groups, it would support the idea that schizophrenia is a syndrome of accelerated aging. However, if differences were observed in the learning deficits between the two groups, it would provide valuable insight into the distinct mechanisms underlying these deficits.

Given the significant diversity of motor symptoms observed in schizophrenia, a fourth objective was to explore the degree to which specific motor behavior deficits are linked to both *positive and negative symptoms* in this disorder.

In conclusion, this non-interventional study aimed to investigate motor learning in schizophrenia and elderly individuals by utilizing a wide array of learning tests. Both *explicit and implicit sequence learning* and *adaptation* were tested. In addition, the broadening of motor learning phenomena has been advocated[37,39] and in this light, *tracking tasks* were included using Circle and Figure Pursuit tasks and *improvement of motor speed and acuity* was examined using a simple aiming task. These sensorimotor learning tasks were complimented with a few cognitive tests and with one of the most sensitive *sensorimotor speed* tests in schizophrenia, i.e., the Symbol

Digit Coding task (SDST), in which the learning of symbol-digit combinations was measured. To facilitate the comparison of these learning tasks, all tasks were executed with the same output apparatus, namely a pen on a digitizing tablet moved by the dominant hand. The basic design of most of the tasks were similar, where individuals were required to make a fast execution of a pen movement to a target out of an array of possible targets. In addition, all participants performed each task.

By comparing our findings with previous hypotheses about the complex psychopathology in schizophrenia, we aspire that our research may contribute to a deeper elucidation of the still poorly understood etiology of the illness. Expanding our knowledge in the psychomotor domain might offer valuable information for targeting the proper brain areas and circuits affected in schizophrenia. This can give direction to subsequent imaging studies and future treatment options in schizophrenia such as targeted medication and rehabilitation programs.

OUTLINE OF THIS THESIS

Each Chapter within this doctoral thesis reflects a specific motor learning paradigm that might be disrupted in schizophrenia. The results of Chapter III-VII have been published in peer reviewed journals. This thesis has been based on the three publications mentioned in Chapter IV - VI. To provide the reader with a complete picture of our entire study on psychomotor learning in schizophrenia and elderly, the results mentioned in Chapter III (De Picker et al. 2014)[61] and in Chapter VII (Hulstijn et al. 2024)[62], are also included in this thesis.

The initial chapter (**Chapter I**) serves as an introduction to motor learning in schizophrenia and offers background information on motor learning in a broader context. This chapter also provides the objectives of this thesis and an overview of the thesis structure.

Chapter II delineates the methodology employed in this thesis, offering detailed insights into the study population, the overall task design, descriptions of the various neuropsychological tests, the kinematic data, and the statistical analysis conducted in this investigation.

The first interventional study (**Chapter III**) encompasses 'simple' motor skill learning comparing the performance of patients with schizophrenia, healthy controls and elderly on two tracking tasks (Circle and Figure Pursuit). In the *Circle Pursuit task*, a target circle, rotating with increasing speed along a predictable circular path on the computer screen, had to be followed by a cursor controlled by the pen on a writing tablet. In the eight-trial *Figure Pursuit task*, participants learned to draw a complex figure by pursuing the target circle that moved along an invisible trajectory between and around several goals. The details of these tasks and the group performances have been published in De Picker et al. (2014).[61]

In **Chapter IV**, processing speed and cognitive learning of symbol-digit associations was measured and compared between patients with schizophrenia, healthy controls and elderly by the Symbol Digit Substitution Test (SDST), an applied coding task requiring participants to write, in 90 seconds, digits under rows of 9 different symbols, according to a key of symbol–digit pairs (which was presented on top of the task sheet). The task was administered on a digitizing tablet, allowing precise

measurements of the time taken to write each digit (writing time) and the time to decode symbols into their corresponding digits (matching time). Details and results of this task have been reported in Cornelis et al. (2014)[63]

In **Chapter V**, implicit motor sequence learning was measured and compared between patients with schizophrenia, healthy controls and elderly. Motor sequence learning was studied earlier by the Figure Pursuit (see Chapter 2) but more extensively in this chapter by the Implicit Pattern Learning Task (IPLT). In the IPLT the cursor had to be moved as quickly as possible from a starting position to a target. The order of the targets on a large part of the trials was fixed and could be learned. This learning was mainly implicit since no learning instructions were given and participants were not informed about the repeated sequence. Fixed sequence trials were intermixed with random trials, and sequence learning was assessed by subtraction of the response time in fixed sequence trials from random trials. Separate analyses of response times and movement accuracy (i.e., directional errors) were performed. Explicit sequence knowledge was assessed using three different awareness tasks. The task and the results obtained with it have been described more elaborately in Cornelis et al. (2016)[64].

Chapter VI aimed at investigating motor adaptation in patients with schizophrenia, healthy controls and elderly. Adaptation learning was measured by the rotation and gain adaptation task and the (more explicit) vertical reversal task. In the *rotation and gain adaptation tasks*, again, participants made fast pen/hand movements from a starting circle towards one of three possible targets. Participants were instructed to move as fast as possible with one simple straight 'shooting' movement. The important difference with the previous tasks was that here, after normal baseline trials, without informing the participants, two perturbations were introduced to which one had to adapt. In the *rotation adaptation task*, adaptation trials consisted of a 30° clockwise rotation around the start position of the cursor relative to the direction of their hand movement. This caused directional errors with the subject finishing next to the target in the direction of the rotation. In the *gain adaptation task* movement feedback was reduced by a factor of 0.7, which caused undershooting and required participants to make a much larger (1/0.7) movement to reach the target. These adaptation trials were immediately followed (again without

informing the participants) by 24 ‘post-adaptation’ trials where the perturbation was completely removed. In the *vertical reversal (mirror) task,* the cursor had to be moved as fast as possible towards one out of three possible targets. The perturbation consisted of the visual feedback of the cursor movement being reversed along the vertical axis, creating a ‘flipped' image as if drawing in a mirror. Participants were fully informed about the onset and offset of the mirroring change in visual feedback. The tasks and the group performances on this task have been reported fully in Cornelis et al. (2021).[65]

Chapter VII provides measures for declarative learning using a verbal learning test and an explicit motor sequence task. Improvement of motor speed and acuity was examined using a single aiming task. In order to contrast the above-mentioned procedural (motor) learning tasks with a standard declarative (verbal) learning task, we used the *California Verbal Learning Test (CVLT).* The CVLT is a neuropsychological test measuring episodic verbal learning and memory using a list of 16 words that read out to the participants five times. Participants are asked after different intervals to recite the words they could recollect and to identify the 16 words in a larger word list. In order to measure explicit motor sequence learning, we utilized the *Explicit Pattern Learning Task (EPLT)*. This task was very similar to the Implicit Pattern/Sequence Learning Task (IPLT) but differed in one important aspect. In the implicit task the next target was always indicated (by a blue color of one the possible target circles) and the participants were not given any instructions about the possibility that a fixed sequence was presented which could be learned. In the explicit version of this task on the other hand instructions were given that the targets are presented in a fixed order which had to be learned. Therefore, the next target was never signaled by a color, but the right target (still an open circle) had to be discovered by trial and error. The *Single Aiming Task* provides a simple measure of psychomotor speed. Single straight lines, differing in orientation, had to be copied as fast as possible with an inking pen on a sheet of paper placed on a digitizing tablet. The task results have been reported in Hulstijn et al. (2024).[62]

Chapter VIII provides a comparative review of the findings elucidated in the preceding Chapters. Moreover, this Chapter delves into the correlations between positive and negative symptoms and the measures of motor learning and performance within the schizophrenia group. A dedicated section is allocated to scrutinizing the cognitive and motor components implicated in motor learning in schizophrenia. Subsequently, the pivotal results are synthesized and discussed in the context of contemporary motor learning theories, with an exploration of the clinical relevance of our findings and directions for future investigations. Finally, the limitations inherent to this thesis are described.

The final parts of this thesis provide a summary in an English (**Chapter IX**) and a Dutch (**Chapter X**) version.

CHAPTER II - METHODS

PARTICIPANTS

Thirty individuals with schizophrenia, 30 healthy controls and 30 elderly volunteers participated in the study (see Table 1). At the time of testing, individuals with schizophrenia were judged to be in a stable clinical condition. The evaluation was done by a trained clinician through subject interview and medical history review. All patients were treated with antipsychotic medication for at least 6 weeks, with no more than two different antipsychotic drugs used at the same time. Patients receiving treatment with benzodiazepines and anticholinergics (including tricyclic antidepressant drugs) were excluded from participating in the study because of their documented negative effects on cognition and sedative effects. Additional inclusion and exclusion criteria for the three participant groups are described in detail in our previously published papers where the same groups of participants were studied (De Picker et al. 2014; Cornelis et al. 2015). Symptom severity of patients was rated by a trained psychology assistant using the scale for the assessment of negative symptoms and positive symptoms (SANS-SAPS)[66,67]. All candidates provided written informed consent. This study was reviewed and approved by the University Hospital of Duffel's Ethics Committee and is registered at ClinicalTrials.gov: NCT01788436. Individuals with schizophrenia were compared with same age controls on several sensorimotor learning tasks. Deficits in schizophrenia were expected particularly on explicit motor learning and on explicit and implicit adaptation tasks. In addition, a group of elderly healthy subjects was included to test if the expected learning deficits in schizophrenia was like the expected deficits in sensorimotor learning of elderly participants.

Table 1. Group characteristics (mean and SD) for all groups and average SANS and SAPS scores in the schizophrenia group.

	Schizophrenia	Elderly	Control	S - C	E - C
N	30	30	30		
Sex (female – male)	10-20	10-20	10-20		
Age (yrs)	36.4 (7.8)	68.7 (5.4)	36.8 (8.6)		
SANS score	26.2 (18.0)				
SAPS score	12.0 (18.5)				
Education years	12.2 (2.4)	14.5 (3.4)	15.1 (2.6)	p < .0001	ns
Adult Reading Test	102.5 (8.0)	111.7 (6.4)	109.8 (4.9)	P = .0001	ns

TASK DESIGN

The investigation of motor learning in this thesis encompassed five out of the six motor learning categories according to Ranganathan et al.[39] (see Table 1, Chapter 1; Table 3 Chapter 2). All five task categories were executed using the same output apparatus—a pen manipulated by the dominant hand on a digitizing writing tablet. While each task was designed to simulate separate learning paradigms, most shared a fundamental design element: participants were required to execute rapid pen movements toward a target from an array of possible targets. This standardized setup allowed for the comparison of various motor learning types. The measurement of coordination typically involves recording at least two distinct movements, which was not feasible in the hospital setting of this investigation, where single pen movement recordings were employed. All participants were screened up to 21 days prior to the first testing session. This screening session involved questionnaires about the in- and exclusion criteria, and the Adult Reading Test (ART), the Wisconsin Card Sorting Test (WCST), and the Letter-Number Sequencing test (LNS; from the WAIS-IV). Following this, there were three testing sessions (each lasting about one hour) which were carried out on day 1, day 2 and day 7. The tasks in the first session were slightly different from those in the second and third sessions (see Table 2 for a timeline of the tasks). All the tasks tested in this thesis are listed in Table 2. All the tasks tested in this thesis are listed in Table 2.

Table 2. Timeline and duration of all experimental learning tasks.

Task	**Time to complete (min)**		
	Day 1	Day 2	Day 7
Digit Symbol Substitution Test (DSST)	2	2	2
Single-Aiming task	3-5	3-4	3
Implicit Pattern Learning Task (IPLT)	8-13	7-8	5-7
Vertical Reversal Task (Mirror drawing)	5-9	4-8	3-5
Pause	10	10	10
California Verbal Learning Test (CVLT)	10	5	5
Explicit Pattern Learning Task (EPLT)	6-7	3-4	3-4
Rotation/Gain Adaptation Task		6-9	5-7
Circle and Figure pursuit	4-6	4-5	4-5
CVLT Delayed Recall and Recognition Test	5		
Total Time including instructions and pauses	61 (55-67)	54 (52-65)	52 (49-65)

Table 3: Learning tasks fitted in the learning categories according to Ranganathan et al.

Motor Learning Category	Instruction	Task	
Improving acuity		Single-Aiming Task	SAT
Sequence learning	Implicit	Implicit Pattern Learning Task	IPLT
	Explicit	Explicit Pattern Learning Task	EPLT
Adaptation		Rotation Adaptation Task	AdapR
		Gain Adaptation Task	AdapG
	Explicit	Vertical Reversal Task	VRT
Tracking		Circle Pursuit Task	PursuitC
+ sequence		Figure Pursuit Task	PursuitF
Applied (writing)		Symbol Digit Substitution Task	SDST writing
Cognitive Learning			
Symbol-digit associations		Symbol Digit Substitution Task	SDST matching
Verbal learning	Explicit	California Verbal Learning Task	CVLT

NEUROPSYCHOLOGICAL TESTS

A comprehensive description of the respective tasks can be found in the following chapters, but a brief description is provided below.

Screening tests

Adult Reading Test - In this task participants had to read aloud a list of words that have atypical grapheme to phoneme translations. Correct pronunciation allows one to measure previous learning of these words. The number of correctly pronounced words were converted to an estimate of pre-morbid IQ.

Wisconsin Card Sorting Test - This task is a neuropsychological test of "set-shifting". Cards varying in shape, number and color had to be sorted by rules that must be learned by trial and error. Once learned the rule is shifted. The number of rules or ‘categories’ completed is a measure of learning speed.

Letter-Number Sequencing test (LNS; from the WAIS-IV) - The LNS was included to gauge working memory. Clusters of letters combined with numbers (e.g., b5n3) were presented auditorily. This had to be repeated in a sequence starting with the numbers in ascending order followed by the letters in alphabetical order.

Line-Copying Task - This task provides a measure of psychomotor speed. Single straight lines, differing in orientation, had to be copied as fast as

possible with an inking pen on a sheet of paper placed on a digitized writing tablet. A more elaborate description of these neuropsychological tests and the obtained group results have been published in De Picker et al.[68].

Verbal learning task

California Verbal Learning Test (CVLT) - The CVLT is a neuropsychological test measuring episodic verbal learning and memory. A list of 16 words is read out to participants five times. Participants are asked immediately following each presentation to recite the words they could recollect (immediate recall; IR). Following an interval of 20-25 minutes (delayed recall; DR) they are again asked to reproduce as many words as possible from the list. After the DR condition, a list of 32 words is read out to them from which they are asked to identify the 16 words of the test list (word recognition; RC). In the second and third session the test list was not presented so there was no immediate recall test; only delayed recall and word recognition were tested.

Sensorimotor learning tasks

In all sensorimotor tasks listed below the same digitizing writing tablet (WACOM 1218RE) was used. For these tasks participants manipulated a non-inking pen to control a cursor visible on a vertical computer screen at the rear of the tablet.

Single-Aiming task (SAT) - To become familiar with the equipment and with the design of the tasks, participants practiced with a single-aiming task. Four possible targets were displayed on the screen as open circles. In each trial a cursor (a turquoise dot 4 mm in diameter) was presented at the previous target location which was marked by a filled yellow circle. Participants were instructed to move the cursor as quickly as possible to the next target, which was indicated by a dark blue circle. A visible square border limited the possible targets to three circles. The trial ended when the cursor was held in that target circle for 100ms, signaled by a short beep and a color change of the target circle to yellow. The order of the targets was random. Task difficulty was manipulated by changing the distance between the circles and circle sizes.

Implicit Pattern Learning Task (IPLT) - As in the SAT, in the IPLT participants were required to move a cursor as quickly as possible from a

starting position to a dark blue target. Again, almost immediately after reaching the target, this circle turned into a turquoise starting position for the next trial. In this task there were 16 possible targets circles positioned in a rhombus of four-by-four circles with equal distances from each other. The targets in baseline and test trials were presented in a random order. Importantly, in this task the order of the targets on a large part of the trials were fixed and could be learned. All intermediate trials were presented in learning blocks, consisting of first eight random targets followed by a fixed 12-target sequence. No learning instructions were given, and participants were not informed about the repeated sequence, therefore learning was implicit. The task with the results obtained have been described more elaborately in Cornelis et al.[64].

Explicit Pattern Learning Task (EPLT) - The EPLT was like the IPLT, however in the explicit version of the task, clear instructions were given to the participants that the targets were presented in a fixed order which had to be learned. The following target was never signaled by a colored circle, rather the correct target had to be discovered by trial and error. As soon as the target was hit, it turned turquoise. After 100ms it changed to yellow signaling that the next target had to be discovered. Target sizes and distances were the same as in the IPLT, but to minimize transfer from the implicit version of the task, the layout of the task and the colors of the target circles were changed. On each trial a square border limited the possible target to three circles. The lines of these square border became thinner after ultimately disappeared. As in the implicit task, the sequence that had to be learned consisted of 12 targets.

Rotation and gain adaptation task - In the adaptation tasks, participants made fast pen/hand movements from a yellow starting circle towards a blue target which was 10 cm away. The starting position was always the same. There were three possible targets (of 25mm diameter) positioned either directly above the starting circle, 45^{o} to the left or 45^{o} to the right of the starting circle. Participants were instructed not to react as quickly as possible but rather to move as fast as possible with one simple straight 'shooting' movement. Following 36 baseline trials, 48 adaptation trials were presented in which visual feedback of the movement was unexpectedly perturbed (rotated or shortened). Participants were not informed of this and had to adapt to these perturbations. In the rotation adaptation task, the

perturbation consisted of a 30° clockwise rotation around the start position of the cursor position on the screen. As a result, to reach the target, pen movements had to be made in a 30° counterclockwise direction. Particularly in the first trials, pen movements started in the wrong direction. Movement time and initial direction errors were the main dependent variables. In the gain adaptation task, the movement of the cursor was reduced by a factor of 0.7, which caused undershooting and required participants to make a much larger (1/0.7) movement to reach the target. These adaptation trials were immediately followed (again without informing the participants) by 24 'post-adaptation' trials where the perturbation was completely removed. A more complete description of these tasks, as well as the results of how well groups adapted to these perturbations can be found in Cornelis et al.[65].

Vertical reversal task (Mirror drawing) - In this task, which might be viewed as an explicit adaptation task, participants had to move a cursor as fast as possible towards a red target circle (10 mm in diameter). Targets were positioned in one of the corners of a 20mm-sided square. The task began with 36 baseline trials. These were followed by 96 perturbation trials in which the visual feedback of the cursor movement was reversed along the vertical axis, creating a 'flipped' image as if drawing in a mirror. The task ended with an additional 60 unperturbed trials. Participants were fully informed about the onset and offset of the mirroring change in visual feedback. The task and the group performances on this task have been reported fully in Cornelis et al.[65].

Circle and Figure pursuit tasks - These two rotary pursuit tasks differed from all previously described sensorimotor tasks. In these tasks, participants had to pursue a continuously moving target by a cursor controlled by the pen on the writing tablet. In the circle pursuit task, a target circle rotated with increasing speed along a predictable circular path on the computer screen. In the eight-trial figure pursuit task, participants learned to draw a complex figure by pursuing the target circle that moved along an invisible trajectory between and around several goals. Details of these tasks and group performances have been published in De Picker et al.[61].

Symbol-Digit Substitution Test (SDST) - The SDST – a reversed version of the classical DSST – is a coding task measuring speed of processing, in which participants are given 90 s to write as many digits as possible under rows of 9 different symbols, following a key of symbol–digit pairs presented at the top of the task sheet (see Figure 1). The task was administered on a digitizing tablet (WACOM 1218RE), allowing precise measurements of the time taken to write each digit (writing time) and the time to decode symbols into their corresponding digits (matching time). Details and results of this task have been reported in Cornelis et al.[63]

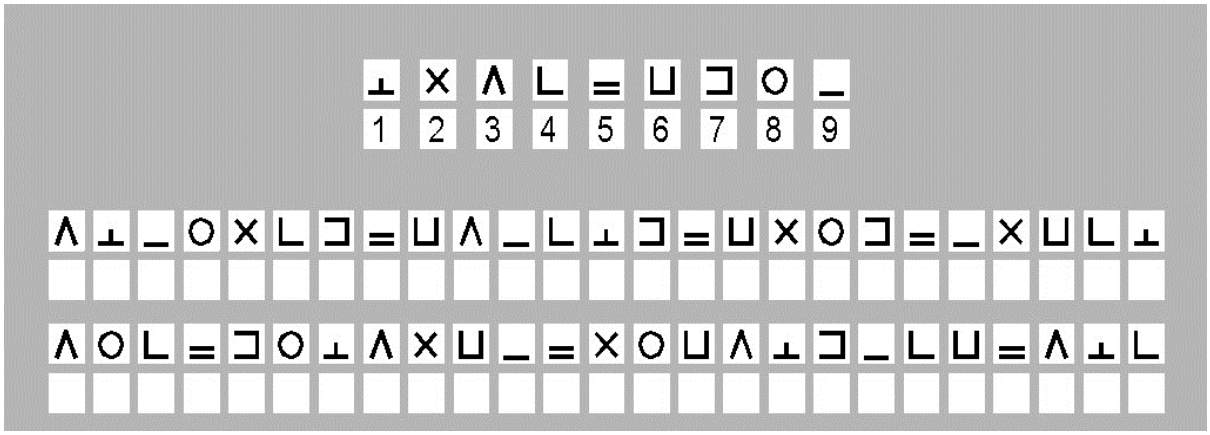

Figure 1. Upper part of the SDST coding sheet.

KINEMATIC DATA

Pen movements were recorded at 200Hz and 0.2mm spatial accuracy. Analysis software was written in MATLAB 7.8.0. Movement Time (MT) was the main dependent variable. It was defined as the time between the crossing of the border of the starting circle and crossing the border of the target circle (see also Figure 1, right panel). On each trial, movements had to end in the target circle in order to start the next trial. Therefore, wrong or inefficient trajectories resulted in a prolonged movement duration. An error was scored when the wrong target was hit. Peaks and valleys in absolute velocity over time were used to segment the entire movement of a trial into a primary movement and any additional submovements. The first minimum in absolute pen velocity after the maximal peak velocity was used as the end of the primary movement (see Figure 1, right panel).

STATISTICAL ANALYSIS

Due to technical errors, the data of a very few participants ($n \leq 4$) are missing in some tasks. All data were analysed in SPSS version 27 with repeated-measures ANOVA's (GLM) on trial blocks as the within-subject factor and groups as the between-subject factor. Group differences with the control group were tested with planned simple contrasts. Bonferroni post hoc analysis was used to compare the schizophrenia with the elderly group. Alpha was set at 0.05.

CHAPTER III - SIMPLE MOTOR SKILL LEARNING

Stable schizophrenia patients learn equally well as age-matched controls and better than elderly controls in two sensorimotor rotary pursuit tasks.

This chapter has been published as:

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Stable schizophrenia patients learn equally well as age-matched controls and better than elderly controls in two sensorimotor rotary pursuit tasks.

ABSTRACT

Objective: To compare sensorimotor performance and learning in stable schizophrenia patients, healthy age- and sex-matched controls and elderly controls on two variations of the rotary pursuit: circle pursuit (true motor learning) and figure pursuit (motor and sequence learning).

Method: In the circle pursuit, a target circle, rotating with increasing speed along a predictable circular path on the computer screen, must be followed by a cursor controlled by a pen on a writing tablet. In the eight-trial figure pursuit, subjects learn to draw a complex figure by pursuing the target circle that moves along an invisible trajectory between and around several goals. Tasks were administered thrice (day 1, day 2, day 7) to 30 patients with stable schizophrenia (S), 30 healthy age- and sex-matched controls (C), and 30 elderly participants (>65 years; E) and recorded with a digitizing tablet and pressure-sensitive pen. The outcome measure accuracy (% of time that cursor is within the target) was used to assess performance.

Results: We observed significant group differences in accuracy, both in circle and figure pursuit tasks ($E<S<C$, $p<0.01$). Strong learning effects were found in each group. Learning curves were similar in circle pursuit but differed between groups in figure pursuit. When corrected for group differences in starting level, the learning gains over the three sessions of schizophrenia patients and age-matched controls were equal and both were larger than those of the elderly controls.

Conclusion: Despite the reduced sensorimotor performance that was found in the schizophrenia patients, their sensorimotor learning seems to be preserved. The relevance of this finding for the evaluation of procedural learning in schizophrenia is discussed. The better performance and learning rate of the patients compared to the elderly controls was unexpected and deserves further study.

INTRODUCTION

The functional outcome of schizophrenia patients is highly impacted by the severity of their cognitive symptoms and their capacity to learn new skills[69]. Two variants of learning are generally distinguished: declarative and procedural learning, the latter referring to skill, habit, or knowledge acquisition that occurs in an implicit manner, i.e., automatically and outside of conscious awareness[70]. Sensorimotor learning, the incremental spatial and temporal accuracy of movements with repetition, represents a form of procedural learning involving different corticostriatal circuits from those in other forms, such as probabilistic classification[71].

Designed as a tool to evaluate motor learning, the rotor pursuit task has been first used in 1947[72]. It measures the ability to keep a stylus on a rotating target, requiring motor control over the proximal upper limb (including shoulder–elbow control and postural control), as well as the ability to continuously process and adapt to sensory (visual and proprioceptive) feedback. Rotor pursuit performance is known to be altered in several pathologies involving the basal ganglia; impaired performance has been demonstrated in Huntington's and Parkinson's disease and enhanced performance in the early trials of the task is seen in patients with obsessive–compulsive disorder[73]. The key substrate of the basal ganglia's involvement in sensorimotor performance and learning is represented by their extensive reciprocal connections to motor and premotor areas of the frontal lobe, implicated in planning and execution of movements[74]. Besides the role of the striatal– cortical circuitry, which is considered particularly important in learning operated through the implicit mode, tracts involving the (pre)motor cortex, the supplementary motor area, and the cerebellum are also implicated in the generation of precise forces and spatial knowledge required for learning new motor skills[75].

In contrast to declarative tasks, in which schizophrenia patients have consistently shown impaired performance and learning compared to healthy controls, procedural learning has been less well studied. Both corticofrontal and striatal involvement are presumed in the pathophysiology of schizophrenia, and abnormal dopamine regulation within the basal ganglia is thought to contribute to the psychotic symptoms of the disease. However, studies examining patients with schizophrenia on

the pursuit rotor motor-skill learning task have so far produced mixed results when comparing both general performance and learning rate of patients to healthy controls (see Table 1)[47,76–82]. Reasons for the conflicting results may reflect methodological differences including in instrumentation, in equating for initial performance, in number of trials administered, or influences of intrinsic moderating variables, such as general intellectual capacity and declarative memory, as well as the effect of psychotropic drugs. It is also debated whether any impaired performance on the rotor pursuit may be related more to underlying psychomotor deficits or to general cognitive decline, both features of schizophrenia[83].

Considering the outcomes of previous studies using the rotor pursuit task in schizophrenia, we hypothesized that true sensorimotor learning would be preserved in schizophrenia patients[47,78,79,81,84]. However, many tasks that measure procedural learning also include a cognitive aspect, e.g., in the form of an implicit sequence to be learned. It has been postulated that motor and cognitive aspects of procedural tasks are governed by different brain processes; motor or skill learning aspects have been associated with a corticostriatal motor circuit involving the putamen, whereas aspects of cognitive or habit learning are suggested to operate the dorsolateral prefrontal cortex circuit involving the caudate[84]. Previous studies that have tried to compare performance on these two aspects have been using combinations of methodologically distinct tasks (e.g., rotor pursuit and a probabilistic classification task, such as the weather prediction task), complicating the direct comparison of their relative outcomes[84]. In this thesis, we aim to assess the cognitive and motor aspects involved in sensorimotor skill learning in the same pursuit task set up, by using two separate task variations, one of which incorporates also a sequence component. Furthermore, a longitudinal set up with repeated sessions over several days offers the added value of distinguishing between early (encoding and acquisition) and late (retention/consolidation) phases of sensorimotor learning, as distinguished in literature[75]. This topic has not been explored in detail.

An age-related decline in sensorimotor performance and learning on the rotor pursuit has been described[85]. Besides the schizophrenia patients and age-matched controls, we, therefore, also included a group of elderly healthy participants to investigate whether the sensorimotor deficits in

schizophrenia patients are comparable to those associated with advanced age. We expected both schizophrenia subjects and elderly participants to perform poorer than young control subjects in the sensorimotor rotary pursuit tasks.

Table 1. Summary of sensorimotor skill studies with Pursuit Rotor task in schizophrenia patients.

Author (year)	**Huston and Shakow (1949)**[7]	**Goldberg et al (1993)**[8]	**Granholm et al (1993)**[9]	**Clare et al (1993)**[10]	**Schwartz et al (1996)**[11]	**Kern et al (1997)**[12]	**Weickert et al (2002)**[13]	**Gomar et al (2011)**[14]
version	contact	contact	photoelectric	not specified	contact	photoelectric	not specified	digital
design	2 blocks x 5 trials x 10sec	3 blocks x 5 trials x 20 sec	6 blocks x 4 trials x 20sec	5 blocks x 6 trials x 20sec	6 blocks x 4 trials x 20sec	6 blocks x 4 trials x 20sec	6 blocks	6 blocks x 4 trials x 20sec
days	d1	d1	d1	d1-d8	d1	d1	d1	d1-d8
N	SZ 122 C 60	24 discordant and 7 normal MZ twin pairs	SZ 11 C 11	SZ 11 C 12	SZ 40 C 40 (each 20 elderly, 20 young)	SZ 18 C 15	SZ 35 C 35	SZ 43 C 22
SZ age mean (range)		31 (17-44)	38.4	42.7 (21-70)	YSZ 33.1 (26-40) ESZ 63.2 (55-70)	36.7	not specified	46.9 (24-64)
SZ sex M:F		14:10	11:0	7:5	38:2	18:0	not specified	34:9
RPM	60	30 and 60	45	30	ESZ 40.50 EC 48.75 YSZ 47.25 YC 56.25	SZ 37.2 C 62.7	not specified	not specified
Trial 1 matched?	no	no	no	no	yes	yes	not specified	yes
IQ matched?	no	no	no	no	no	no	yes (subsample n=14)	yes (subsample n=22)
Absolute performance difference	SZ<C	SZ=C	SZ=C	SZ<C	SZ<C	SZ=C	SZ<C; IQmatched SZ=C	SZ<C; IQmatched SZ=C
Learning rate difference	not specified	not specified	SZ=C	SZ=C	SZ<C	SZ=C	SZ=C	SZ=C

SZ = schizophrenia patients; C = controls; ESZ = elderly schizophrenia patients; EC = elderly controls; YSZ = young schizophrenia patients; YC = young controls; RPM = rotations per minute.

MATERIALS AND METHODS

Study design

For all subjects enrolled, the study consisted of an eligibility screening examination (up to 21 days prior) and three cognitive assessment days. The screening examination included baseline assessments of executive functioning (Wisconsin Card Sorting Test; WCST), premorbid IQ (Dutch Adult Reading Test/Nederlandse Leestest voor Volwassenen; NLV), and psychomotor speed (measured with a line-copying task on a digitizing tablet; LCT).

Cognitive assessments were made in two subsequent sessions (days 1 and 2), which were separated by overnight sleep. An additional third session was performed on day 7. The pursuit task was part of a cognitive test battery of approximately 90 min that was administered to all subjects in the same way and will be reported elsewhere. The time of day for completion of the cognitive test batteries was comparable on all test days for each subject, but not identical for all subjects.

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices, applicable regulatory requirements, and in compliance with the study protocol. The study protocol was reviewed and approved by the Institutional Ethics Committee.

Participants

After giving written informed consent, subjects were screened to ascertain their eligibility for the study according to the in- and exclusion criteria specific for the population enrolled. The patient sample consisted of 30 outpatients aged 18–55 with a known history of schizophrenia or schizo-affective disorder (based on DSM-IV criteria) of at least 12 months, as confirmed by the referring psychiatrist. Exclusion criteria were current use of drugs with anticholinergic properties (including tricyclic antidepressants) and benzodiazepines, or comorbid DSM-IV diagnosis of substance dependence within 3 months prior to screening evaluation (except for caffeine and nicotine dependence); patients with a positive drug screen at screening could be included provided they did not meet DSM-IV diagnosis of substance dependence and consented to abstain from illegal

drugs at any time during the study. An alcohol breath test and urine drug screening were performed at each of the cognitive assay days. All patients were stably treated with antipsychotic medication for at least 6 weeks, with no more than two different antipsychotic drugs used concurrently. Patients were judged to be in stable clinical condition at the time of testing through subject interview and medical history review by a trained clinician. Symptom severity of patients was rated at screening by a trained psychology assistant using the scale for the assessment of negative symptoms and positive symptoms (SANS-SAPS)[67].

Thirty age- and gender-matched control participants, as well as 30 gender-matched elderly participants (>65 years of age) were recruited from the local community. They met the same exclusion criteria as the patients. They were also interviewed by a clinician to verify that they had no personal history of psychiatric disorders nor first-degree relatives with psychotic disorders and that they were not using any psychotropic medication.

Pursuit task setup

Based on the classical rotary pursuit task[86], our pursuit rotor (PR) continuous sensorimotor tasks required subjects to follow the movements of a target circle (12mm in diameter) on the computer screen with a cursor they could control by manipulating a pressure-sensitive pen on a digitizing writing tablet (WACOM1218RE), recording at 200 Hz frequency and 0.2mm spatial accuracy.

In the *circle pursuit (CPR) task*, the target circle rotates along a predictable circular path with a radius of 7.5 cm (see Figure 1). This task consisted of two trials of 30 s duration with six rotations each. The speed of the target was gradually increased from10 s per 360° rotation (6 RPM) to 3 s per full rotation (20 RPM).

The CPR was directly followed by the *figure pursuit (FPR) task* in which subjects had to follow a trajectory between and around several on-screen goals (see Figure 2). This task can be perceived as learning to draw a complex figure in a so-called “pursuit” condition in which a person is asked to keep the pen cursor on a target circle that moves along the (invisible) trajectory that had to be learned. The start and end positions of the sequence are marked by white and black circles, signaling with a high and

low beep, respectively, when the cursor reaches them. This task consisted of eight identical trials of 10 s duration.

Both during circle and figure pursuit, subjects were able to follow their level of performance throughout the task, with vertical score bars appearing on the right side of the screen after each trial, indicating their relative level of target contact (see Figures 1and 2). The dependent variable in both task variations was accuracy (% of time that the cursor is within the target circle, higher numbers indicating better performance). The total time of the PR tasks was approximately 3 min.

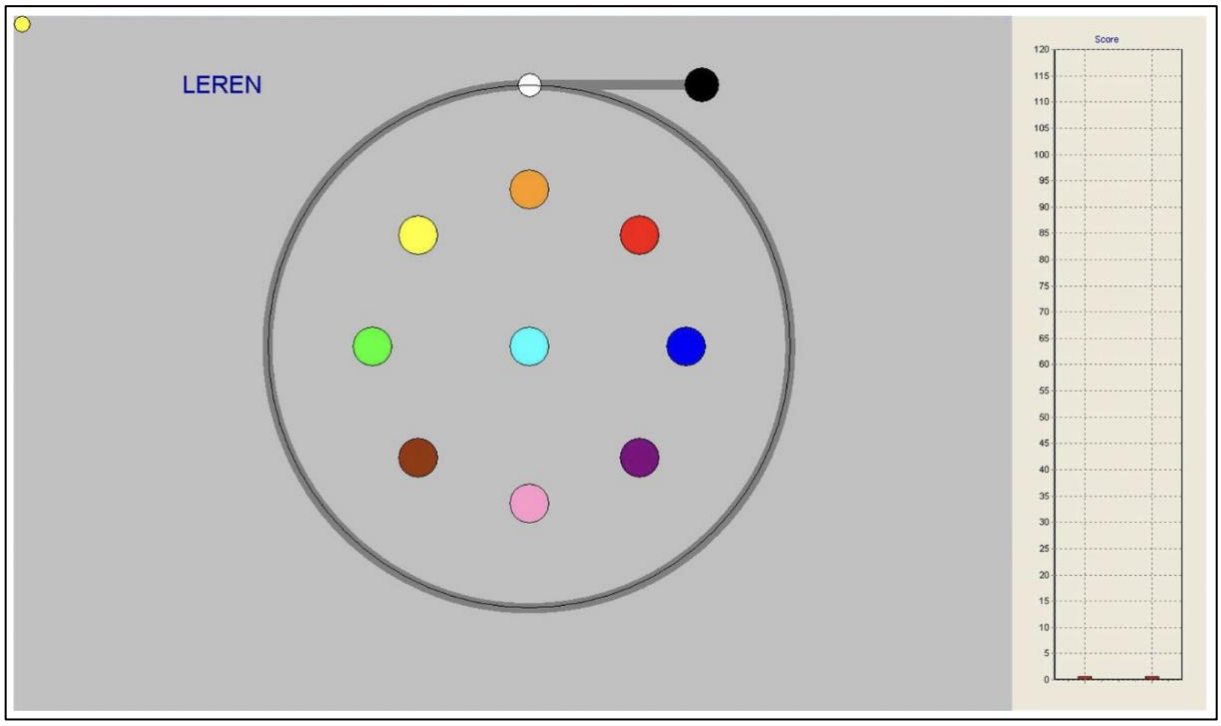

Figure 1: Circle pursuit task on-screen, gray line indicating pursuit trajectory, not seen by participants. On the right-hand side, performance barsappeared as feedback after each trial.

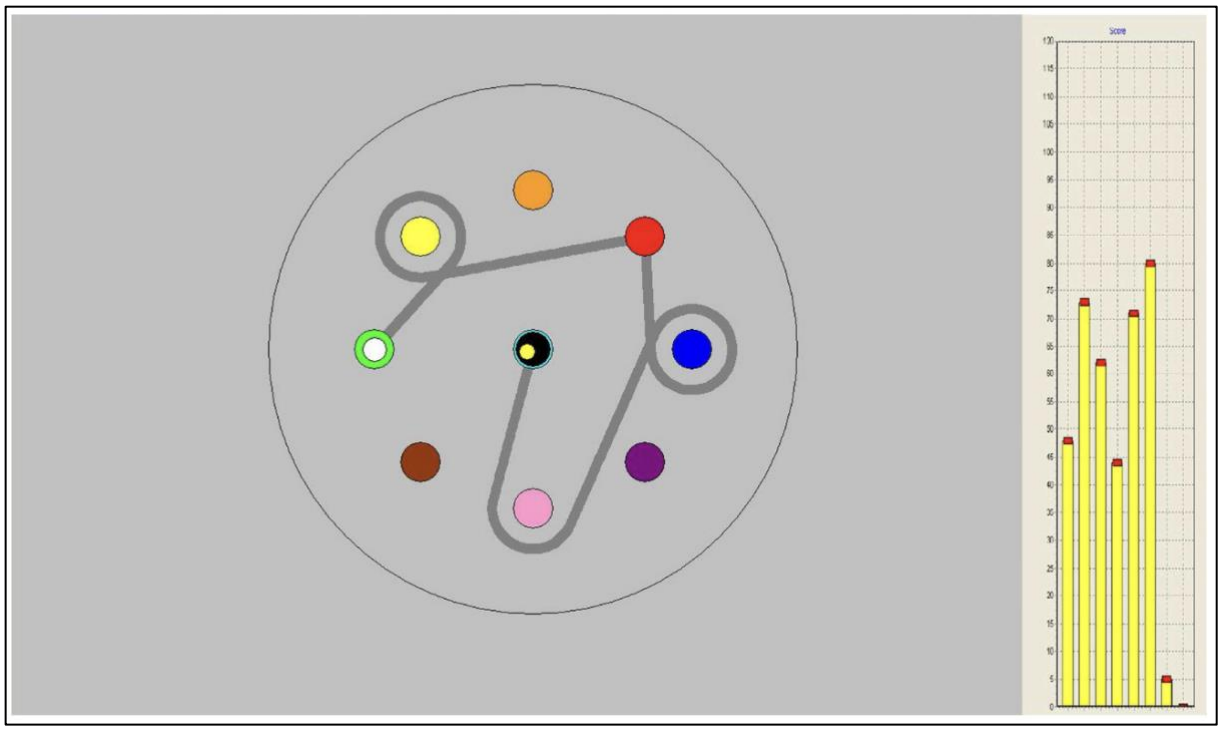

Figure 2: Figure pursuit task on-screen, gray line indicating pursuit trajectory, not seen by participants. On the right-hand side, performance bars appeared as feedback after each trial.

Statistical analysis

We performed all statistical analyses in IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY, USA). Demographic features and baseline assessment results were analyzed using independent samples T-tests to evaluate significant group differences. There were some missing data for the Y group on the LCT (n =3) and for the E group on the WCST (n =2) and the LNS (n =1). WCST outcome was defined as the number of categories completed. The movement time (MT) on the LCT was chosen as the relevant outcome measure for psychomotor speed.

The PR performance was quantified by the variable accuracy and measured in three groups (schizophrenia patients=S, young controls=C, elderly participants=E). We tested everyone repeatedly in three sessions (day 1, day 2, day 7). Within each session, several identical trials were performed (two trials in CPR, eight trials in FPR). There were no missing data on the PR tasks. To provide a measure for learning over sessions, we computed two learning measures for each session: the mean and the cumulative learning gain, the latter correcting for the participant's starting level (performance on the first trial in the first session). In the figure pursuit, the

cumulative learning gain was calculated as (T1+T2+T3+T4+T5+T6+T7+T8)/8-S1T1. In circle pursuit, this was (T1+T2)/2-S1T1.

We analyzed the PR data using a general linear model (GLM) with repeated measures. Because the time variable is accounted for by two separate variables in our study design, we first conducted an overall analysis with two within-subjects factors (Session Number, Trial Number) and one between-subjects factor (Group, three levels). A post hoc analysis was used to contrast the three study groups, using Bonferroni correction to adjust for multiple comparisons (Analyses 1 and 2). In the second step, we applied separate GLM repeated measures analyses to compare the learning over trials of groups Y–S and Y–E within the first session, which we expected to express the greatest learning effect. Subsequently, we compared the between-subjects effects of group in this analysis to the effects of group in a second analysis accounting for a covariate variable that was expected to influence the between-group differences (Analyses 3 and 4).

This procedure was repeated for three different covariates: LCT movement time (LCT_MT, an estimate of motor speed), WCST categories completed (WCST_cat, a measure of executive functioning), and education years. In the third step, we used the computed learning measures (mean and cumulative learning gain) in separate GLM repeated measures analyses to evaluate the learning across sessions between groups Y–S and Y–E (Analyses 5 and 6).

RESULTS

Demographics and baseline assessments

Demographic features, baseline assessment results and group differences are summarized in Table 2. Schizophrenia patients (S) had a significantly lower level of education and premorbid IQ compared to the young controls (Y), whereas the young controls and elderly participants (E) did not differ significantly for this parameter. The Y group significantly outperformed both E and S groups on the LCT and WCST measures (see Table 2). Composite symptom scores for schizophrenia patients were 25.67±17.39 on the SANS scale and 14.24±19.68 on the SAPS scale.

A summary of the use of antipsychotic drugs in schizophrenia patients included in the study is provided in Table 3.

Table 2: Demographic and baseline assessment results

	Schizophrenia Patients (S)	Young Controls (Y)	Elderly Participants (E)	T-test S-Y	T-test E-Y
N	30	30	30	Matched	Matched
Age; mean (range)	36.4 (23-53)	37.3 (18-52)	69.2 (65-79)	$t(58) = 0.16$ $p = .875$	$t(58) = 18.99$ $p < .001$**
Sex M:F	20:10	20:10	20:10	Matched	Matched
Education years; mean (SD)	12.2 (+/-2.4)	15.1 (+/-2.6)	14.5 (+/-3.4)	$t(58) = 4.50$ $p < .001$**	$t(58) = 0.74$ $p = .465$
NLV Premorbid IQ; mean (SD)	101.30 (+/-10.29)	110.07 (+/-6.39)	111.73 (+/-6.43)	$t(58) = 3.96$ $p < .001$**	$t(58) = 1.01$ $p = .318$
LCT movement time; mean (SD)	0.36 (+/-0.15)	0.27 (+/-0.12)	0.40 (+/-0.13)	$t(55) = 2.40$ $p = .020$*	$t(55) = 3.65$ $p = .001$**
WCST categories completed; median (range)	3 (0-5)	5 (0-5)	3 (0-6)	$t(58) = 2.60$ $p = .012$*	$t(56) = 3.35$ $p = .001$**

NLV (Dutch Adult Reading Test/Nederlandse Leestest voor Volwassenen); LCT (Line Copying-Task); WCST (Wisconsin Card Sorting Test); T-test differences are reported as t(df) and p-values (* significant at the 0.05 level; ** significant at the 0.01 level).

Table 3: Antipsychotic drug prescriptions in schizophrenia patients

Antipsychotic drug name	Number of prescriptions	Dose range
Clozapine	8	50-700 mg/d
Amisulpiride	7	200-800 mg/d
Haloperidol decanoate	7	75-200 mg/m
Quetiapine	6	50-600 mg/d
Olanzapine	3	5-20 mg/d
Paliperidone	3	3-6 mg/d
Paliperidone depot	3	75-200 mg/m
Aripiprazole	2	10-30 mg/d
Olanzapine depot	2	210-405 mg/m
Risperidone depot	2	50 mg/m
Clotiapine	1	40 mg/d
Flupentixol	1	1 mg/d
Bromperidol decanoate	1	125 mg/m
Zuclopentixol depot	1	200 mg/m
Risperidone	1	4 mg/d

Analyses of circle and figure pursuit

Learning the PR tasks over all trials and sessions

In Analysis 1, independent of groups, learning effects were demonstrated by significant main effects of TrialNumber and SessionNumber and a significant interaction TrialNumber* SessionNumber both in the CPR task and the FPR task, indicating that the learning curves over trials for each session were different [see Table 4A].

Upon addition of Group as between-subjects factor in analysis 2, in both PR tasks, a significant main effect of Group was found [see Table 4A]. Post hoc analysis with Bonferroni correction demonstrated that the performance of schizophrenia patients and elderly participants was significantly poorer than the young control subjects at all stages of the task ($p < 0.001$), and that the elderly participants were the worst performing group (E-S CPR mean difference −13.62, SE 3.11, $p < 0.001$; E-S FPR mean difference −14.42, SE 2.97, $p < 0.001$).

In contrast, the interaction of TrialNumber*SessionNumber*Group was only significant in FPR, indicating that the learning curves of the groups also followed different slopes (with significant linear, quadratic, and cubic components). In CPR, the slopes were similar for the three groups [see Table 4A; Figures 3 and 4].

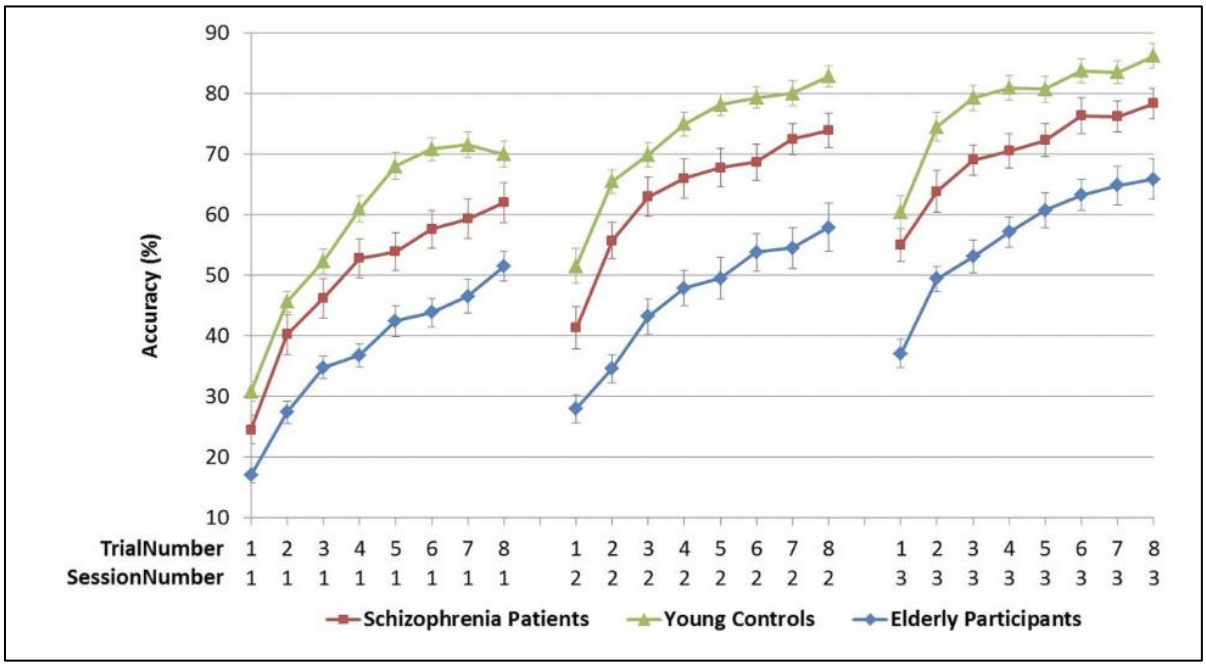

Figure 3: Figure pursuit accuracy over three sessions and eight trials.

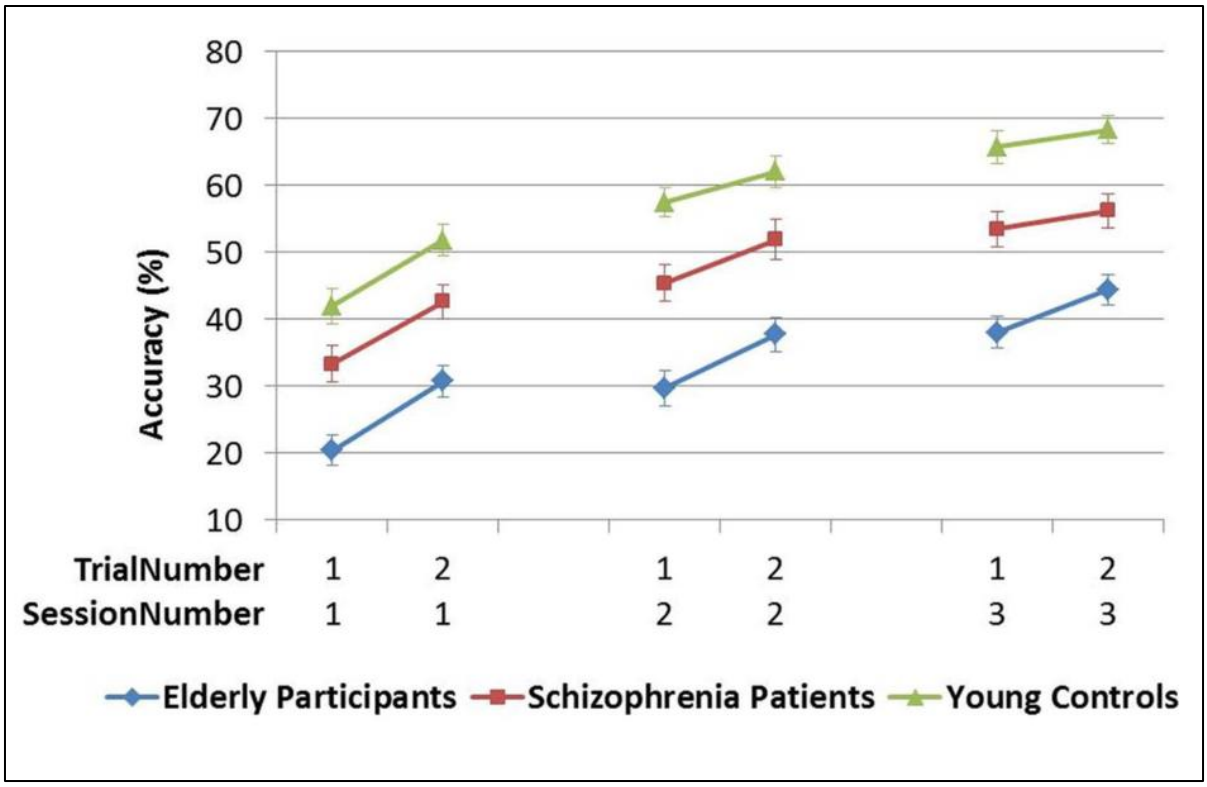

Figure 4: Circle pursuit accuracy over three sessions and two trials.

Learning the PR tasks over trials within session 1

In Analysis 3, comparisons of groups Y–S and Y–E on the FPR session 1 showed both a difference in performance, indicated by the significant between-subjects effect of the Group variable, as well as a different learning slope over trials, indicated by the significant TrialNumber*Group interaction. However, the significant Y–S group effect was reduced to a non-significant value when accounting for significant covariates: LCT_MT, WCST_cat, and education years in Analysis 4 [see Table 4B]. Combination of two individually significant covariates (LCT_MT plus WCST_cat and LCT_MT plus education years) further reduced the FPR Group effect.

In CPR session 1, again there was only a significant between subjects' effect of Group without TrialNumber*Group interaction. Furthermore, only the WCST_cat covariate reached a level of significance in the between-groups effect in this task, reducing also the Group difference between Y and S to a non-significant level [see Table 4B].

Interestingly, when these same covariates were added to the Y–E comparison, in both PR tasks the between-subjects Group effect remained significant [see Table 4B].

None of the analyses with covariates demonstrated a significant TrialNumber*Covariate or Group*Covariate interaction, suggesting the main effects of the covariates on the Accuracy variable can be interpreted independently of Group or Trial number.

Learning the PR tasks over sessions

The mean accuracy over trials was compared across sessions 1– 3 in Analysis 5. In both PR tasks, a difference in performance between Y–S and Y–E groups was observed (i.e., significant main between-subjects effect of Group), but the Session Number*Group interaction was only significant for Y–E comparison, suggesting that schizophrenia patients showed a similar learning pattern across sessions as did young controls, but elderly participants did not [see Table 4C; Figures 5 and 6].

In Analysis 6, the same analyses were repeated with the learning measure cumulative learning gain, which corrects the mean for the participant's starting level performance on the first trial in session 1. Here, when Y and S groups were compared, neither the Session Number*Group interaction nor the between-subjects effect of Group was significant in either of the PR tasks. In the comparison of Y and E groups, a significant interaction of Session Number*Group was maintained for both PR tasks, but the main effect of Group was only significant for FPR [see Table 4C; Figures 3 and 4].

Table 4. Results of the GLM repeated measures analyses

Table 4a	**Figure Pursuit**		**Circle Pursuit**	
Y, S and E groups	*F* (hypothesis df, error df)°	*p*	*F* (hypothesis df, error df)°	*p*
SessionNumber[1]	285.76 (2, 88)	< .001**	173.36 (2, 88)	< .001**
TrialNumber[1]	179.77 (7, 83)	< .001**	140.82 (1, 89)	< .001**
SessionNumber*TrialNumber[1]	4.17 (14, 76)	< .001**	13.34 (2, 88)	< .001**
Group[2]	31.59	< .001**	30.80	< .001**
SessionNumber*TrialNumber*Group[2]	1.97 (28, 148)	.005**	0.54 (4, 172)	.710

Table 4b		**Figure Pursuit**		**Circle Pursuit**	
Session 1, Y group – S group		*F* (hypothesis df, error df)°	*p*	*F* (hypothesis df, error df)°	*p*
TrialNumber*Group[3]		2.80 (7, 52)	.015*	0.07 (1, 58)	.799
Group[3]		7.80	.007**	6.51	.013*
With Covariate					
WCST_cat	Covariate[4]	19.42	< .001**	9.35	.003**
	Group[4]	4.57	.114	2.54	.117
LCT_MT	Covariate[4]	7.32	.009**	3.15	.082
	Group[4]	2.98	.090	3.03	.087
Education years	Covariate[4]	4.97	.030*	2.18	.146
	Group[4]	1.82	.183	1.84	.181
WCST(1) + LCT_MT(2)	Covariate1[4]	16.33	< .001**		
	Covariate2[4]	5.84	.010**		
	Group[4]	0.67	.418		
Education years(1) + LCT_MT(2)	Covariate1[4]	5.48	.023*		
	Covariate2[4]	8.86	.004**		
	Group[4]	0.17	.685		
Session 1, Y group – E group		*F* (hypothesis df, error df)°	*p*	*F* (hypothesis df, error df)°	*p*
TrialNumber*Group[3]		3.42 (7, 52)	.004**	0.08 (1, 58)	.775
Group[3]		85.77	< .001**	43.63	< .001**
With Covariate					
WCST_cat	Covariate[4]	9.01	.004**	6.84	.011*
	Group[4]	61.35	< .001**	27.38	< .001**
LCT_MT	Covariate[4]	5.24	.024*	0.61	.439
	Group[4]	52.51	< .001**	27.55	< .001**

Table 4c		Figure Pursuit		Circle Pursuit	
Learning Measure over sessions		*F* (hypothesis df, error df)°	*p*	*F* (hypothesis df, error df)°	*p*
	Y, S and E groups				
	SessionNumber*Group[5]	2.51 (4, 172)	.043*	1.59 (4, 172)	.179
	Group[5]	31.59	< .001**	30.80	< .001**
	Y group –S group				
Mean	SessionNumber*Group[5]	0.10 (2, 57)	.905	0.87 (2, 57)	.424
	Group[5]	9.16	.004**	11.74	.001**
	Y group – E group				
	SessionNumber*Group[5]	3.42 (2, 57)	.039*	3.19 (2, 57)	.049*
	Group[5]	83.78	< .001**	70.26	< .001**
Cumu-lative Lear-ning Gain	**Y, S and E groups**				
	SessionNumber*Group[6]	2.51 (4, 172)	.043*	1.59 (4, 172)	.179
	Group[6]	7.81	.001**	1.54	.220
	Y group – S group				
	SessionNumber*Group[6]	0.10 (2, 57)	.905	0.87 (2, 57)	.424
	Group[6]	1.04	.312	1.50	.225
	Y group – E group				
	SessionNumber*Group[6]	3.42 (2, 57)	.039*	3.19 (2, 57)	.049*
	Group[6]	16.23	< .001**	0.269	.107

Wilk's Lambda F for multivariate analysis results; * significant at the 0.05 level; ** significant at the 0.01 level

[1] analysis 1: within-subjects factors SessionNumber(3) and TrialNumber (8 FPR; 2 CPR);
[2] analysis 2: within-subjects factors SessionNumber(3) and TrialNumber (8 FPR; 2 CPR) and between-subjects factor Group (3)
[3] analysis 3: within-subjects factor TrialNumber (8 FPR; 2 CPR) and between-subjects factor Group (2);
[4] analysis 4: within-subjects factor TrialNumber (8 FPR; 2 CPR), between-subjects factor Group (2) and covariate;
[5] analysis 5: within-subjects factor SessionNumber(3), between-subjects factor Group (3 or 2), variable Mean
[6] analysis 6: within-subjects factor SessionNumber(3), between-subjects factor Group (3 or 2), variable Cumulative learning gain

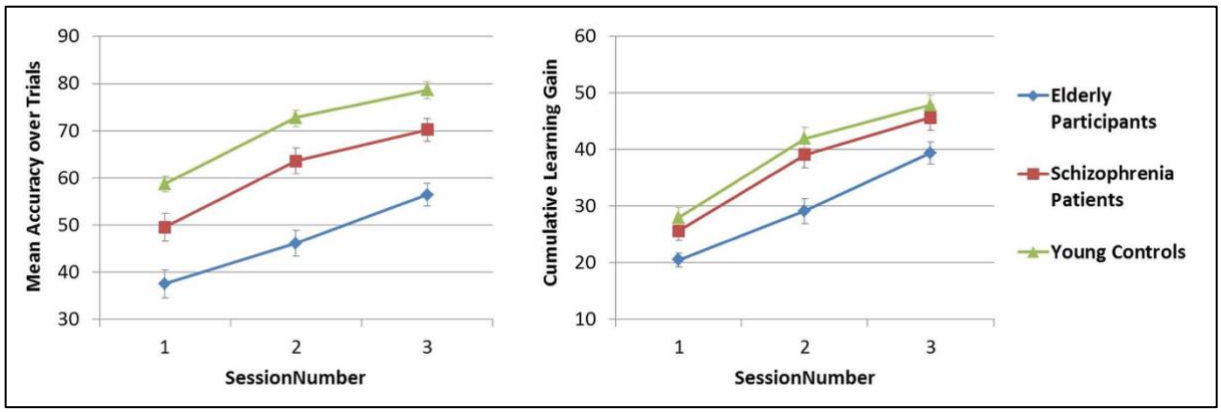

Figure 5: Figure pursuit mean accuracy and cumulative learning gain over three sessions

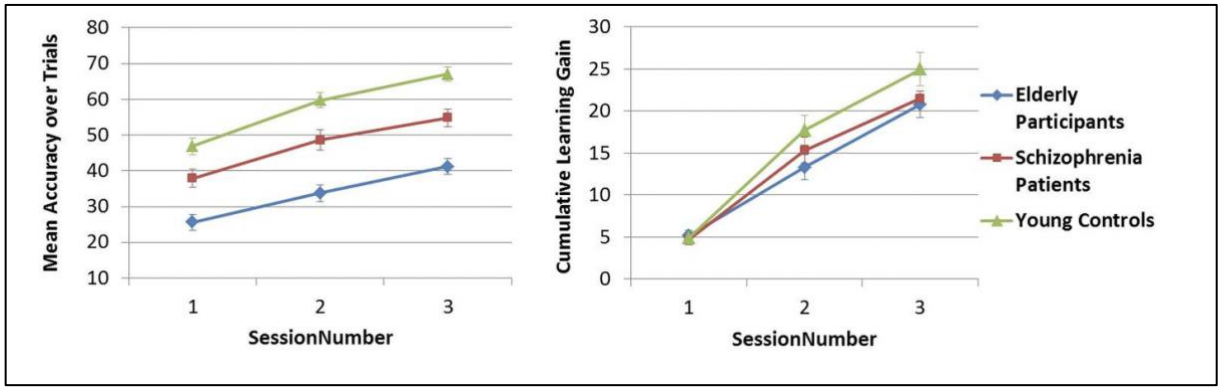

Figure 6: Circle pursuit mean accuracy and cumulative learning gain over three sessions.

DISCUSSION

Key results

General performance - Our results demonstrate poorer performance both in schizophrenia patients and in elderly participants compared to young controls, thereby matching findings of previous rotary pursuit studies[47,76,79,80,82,85]. This finding was observed in both pursuit tasks, and both on a within- and across-session level.

In *FPR* session 1, the poorer performance in patients was found to be attributable to differences in other functional parameters, such as psychomotor speed (LCT_MT), executive functioning (WCST categories completed), and years of education, with an additive effect. This implies that patients performing worse than healthy controls on the FPR task also perform worse on one or several of these baseline measures. One could thus hypothesize that the impaired FPR performance of patients is caused by reduced psychomotor speed and/or executive functioning or a lower level of education. Alternatively, it could also point out the existence of a separate subgroup of schizophrenia patients exhibiting impairments on all these domains.

In contrast, the difference in FPR performance between elderly participants and young controls could not be accounted for by differences in psychomotor speed nor executive functioning, indicating a performance gap between these groups that is independent of other functional parameters.

In *CPR*, contrasting to what was expected, psychomotor speed did not have a significant effect on the performance in session 1. Only executive functioning level appeared to account significantly for the difference between schizophrenia patients and controls in this task.

After the mean performance per session was corrected for the initial starting level, there was no longer a significant difference in performance across sessions between patients and controls. This finding suggests that the lower mean performance of patients is caused by a significantly lower starting level, which is not recovered by additional practice. However, in two other recent PR studies, an individual equation of the target speed was applied to account for participants' starting level performance; yet the

general performance in schizophrenia patients was found to be impaired nonetheless[80,87]. Thus, adjusting the difficulty of the task does not seem to solve the performance gap. Further study is needed to understand these seemingly contradictory findings.

Regarding the elderly participants, their poorer mean level of performance was amended in the CPR but remained in the FPR after correction for their significantly lower starting level by the cumulative learning gain measure.

Skill learning rate - We have established that all groups learned the new FPR and CPR sensorimotor skills over trials and sessions, but whereas the overall learning rate of schizophrenia patients and elderly participants was preserved in CPR, it differed between the three groups in FPR.

The early phase of learning the FPR skill was characterized by a significantly different learning curve of the schizophrenia patients and the elderly participants compared to young controls, who reached their peak performance earlier, as illustrated in Figure 3.

The CPR consisted of only two trials in the first session, and therefore by definition the learning rate was marked by a linear increase, of which the slopes did not differ between the three groups (see Figure 4). In the later phase of learning of both PR tasks, schizophrenia patients and control subjects showed comparable learning gains over sessions, but elderly participants learned significantly less.

Study limitations

By using two variations of the PR task, we have attempted to distinguish motor and sequence learning components, yet it remains difficult to single out and evaluate separately the processes involved in sensorimotor learning and performance. We cannot rule out the impact of declarative and spatial memory, attention capacity, and motor coordination on our PR skill performance and learning results.

Also, while our CPR task was similar to the classical rotary pursuit task, we used a different methodology regarding the number of trials and rotation speed (see Table 1), which complicates the comparison of our results in the CPR to those of previous PR studies. It is possible that the number of trials

per session in our CPR was too limited to establish within- session learning differences, which were found in FPR but not in CPR.

This study included only schizophrenia outpatients who were able to complete the test batteries and results can, therefore, not necessarily be generalized to the whole population of patients with schizophrenia. However, the mean SAPS and SANS composite scores in our sample concurred with scores found by van Erp et al. in a sample of 205 schizophrenia patients: mean composite SAPS 16.8±14.2 compared to 14.2±19.7 in our sample and mean composite SANS 23.0±14.6 compared to 25.7±17.4 in our sample[88]. Our patient population can, therefore, not be presumed to differ significantly in terms of symptom severity from other schizophrenia patient samples.

A large within-group heterogeneity in performance existed, particularly in the starting performance level of schizophrenia patients and the final performance level of elderly subjects. The relatively higher performance heterogeneity of the patients and elderly participants compared to the young controls may imply performance on the PR tasks in these groups was influenced by other variables than those accounted for in our study design.

Problems with the evaluation of cognition of schizophrenia patients include lack of motivation and attention problems caused by negative symptomatology. Patients were instructed to complete the tasks to the best of their ability and our experience during test procedures was that being able to follow the feedback of their performance live on-screen provided an additional stimulus for performance optimization to subjects in all groups.

Other variables that may affect task performance include general cognitive functioning and medication use. We did not evaluate the study groups for their current IQ scores, and the schizophrenia patients had a significantly lower premorbid IQ score compared to young and elderly controls. In previous studies, comparing IQ- matched subgroups reduced or abolished differences in the overall level of performance between schizophrenic patients and control subjects on the rotor pursuit and other tasks of procedural learning[47,82]. However, IQ matching may also introduce a bias, considering research of general intelligence in schizophrenia has shown that only about a quarter of schizophrenia patients have a preserved IQ compared to the general population[89]. Moreover, correlations between

motor and cognitive functioning in schizophrenia patients have been repeatedly demonstrated[90,91], and matching for cognitive parameters in studies of motor learning may, therefore, greatly influence the primary outcome measure.

It is often argued that cognitive impairments in schizophrenia, and specifically psychomotor ones, are caused by psychotropic substances in general and antipsychotic medication. All patients in our study had been stably treated with antipsychotic medication at the time of testing, and 16 patients were using more than one antipsychotic drug concomitantly (see Table 3). The reduced performance on PR tasks combined with a normal learning rate in patients may be hypothesized to be due to the use of antipsychotic drugs, known to affect psychomotor functioning[92].

Implications for future research and clinical perspectives

Our study provides important caveats toward future research on procedural learning in schizophrenia. Researchers should be aware that motor tasks including a sequence component should be distinguished from true motor learning tasks.

As shown in this study, small variations applied to commonly used procedural tasks may allow to distinguish between operationally different components that may be important to further elucidate the nature of the deficits in schizophrenia. Particularly, the combination of different sensorimotor learning tasks with imaging techniques can be valuable to evaluate structural and functional brain alterations in the motor system.

Furthermore, a longitudinal design should be a key feature of any study design interested in aspects of learning and memory, with differentiation of early and late learning phases.

Cognitive functioning, and specifically also executive functioning as measured with the Wisconsin card sorting test, has been shown to be a major predictor of functional outcome in schizophrenia[69]. Motor learning in schizophrenia has been less studied, and its relation to functional outcome is currently unknown. However, evidence that motor performance is not only related to cognitive and executive functioning but also a predictor of cognitive deficits in schizophrenia patients at 1-year follow-up[90] suggests

an association between motor performance or learning capacity, and functional outcome may exist meriting further investigation.

An age-related decline in sensorimotor learning has been previously recognized[85,93], and in our study indeed the elderly participants demonstrated both poorer performance and lower learning gains in both PR tasks. Unexpectedly, the schizophrenia patients even outperformed the elderly healthy participants. Although this finding needs to be confirmed, it governs a more optimistic message about the functioning of patients than has hitherto been assumed. However, it is uncertain whether this pattern is maintained throughout different cognitive domains. Findings of our research group[63], suggest that in other cognitive domains, elderly participants may outperform schizophrenia patients. It might be interesting for future studies to include both elderly and non-elderly schizophrenia and control participants to differentiate between the mechanisms of cognitive impairment related to ageing and schizophrenia.

A generally lower level of performance in schizophrenia (starting and ending the learning phase at a lower level than control subjects) has been a frequent finding in PR studies[79,80,82]. Some authors have interpreted this phenomenon as reflecting impaired procedural learning in schizophrenia patients. However, since this reduced overall level of performance is usually accompanied with a normal learning rate, the mechanisms that underlie these two aspects of task performance are likely to differ to some extent. Because of this difficulty to differentiate between y-intercept (absolute performance) and slope (learning rate), and because of the high degree of within-group heterogeneity on performance level, many studies have not been able to conclude as to the actual capacity for sensorimotor skill learning of schizophrenia patients. Based on our results, it seems that schizophrenia patients have a mostly preserved capacity to learn sensorimotor skills, with any deficit related more to the early learning phase of sequence-holding skills and depending largely on the starting level performance of patients. This knowledge may prove important to the development and evaluation of therapies to improve such deficits in schizophrenia, in which the rotary pursuit, a well- established, easy and quick to administer task, may be used for the initial and follow-up evaluation of motor learning capacity and performance in patients.

Because the late-phase learning of patients was preserved, it can be suspected that with an extended number of trials, the patients could eventually reach the same performance level as the final level in young controls. Thus, schizophrenia patients maintain the ability to acquire new skills, of vital importance to everyday functioning, given extra room for rehearsal.

On the other hand, since more complex skills often also require additional cognitive components related to planning and organization, it is unclear whether this finding may be translated to all real-life skills.

CONCLUSION

Both in circle pursuit (motor task) and figure pursuit (motor plus sequence task), learning was evident in all groups, with equal learning gains of schizophrenia patients compared to age-matched controls, but reduced learning in elderly participants. In terms of general performance, the schizophrenia patients fell between the young controls and the elderly participants, differing significantly from both. Our results suggest that the lower performance of schizophrenia patients compared to age-matched controls can be accounted for by impaired speed of movement and executive functioning.

CHAPTER IV - APPLIED MOTOR LEARNING

Preserved learning during the symbol-digit substitution test in patients with schizophrenia, age-matched controls and elderly.

This chapter has been published as:

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Preserved learning during the symbol-digit substitution test in patients with schizophrenia, age-matched controls and elderly.

ABSTRACT

Objective: Speed of processing, one of the main cognitive deficits in schizophrenia is most frequently measured with a digit–symbol-coding test. Performance on this test is additionally affected by writing speed and the rate at which symbol–digit relationships are learned, two factors that may be impaired in schizophrenia. This study aims to investigate the effects of sensorimotor speed, short-term learning, and long-term learning on task performance in schizophrenia. In addition, the study aims to explore differences in learning effects between patients with schizophrenia and elderly individuals.

Methods: Patients with schizophrenia (N=30) were compared with age-matched healthy controls (N=30) and healthy elderly volunteers (N=30) during the Symbol-Digit-Substitution Test (SDST). The task was administered on a digitizing tablet, allowing precise measurements of the time taken to write each digit (writing time) and the time to decode symbols into their corresponding digits (matching time). The SDST was administered on three separate days (day 1, day 2, day 7). Symbol–digit repetitions during the task represented short-term learning and repeating the task on different days represented long-term learning.

Results: The repetition of the same symbol–digit combinations within one test and the repetition of the test over days resulted in significant decreases in matching time. Interestingly, these short-term and long-term learning effects were about equal among the three groups. Individual participants showed a large variation in the rate of short-term learning. In general, patients with schizophrenia had the longest matching time whereas the elderly had the longest writing time. Writing time remained the same over repeated testing.

Conclusion: The rate of learning and sensorimotor speed was found to have a substantial influence on the SDST score. However, a large individual variation in learning rate should be considered in the interpretation of task

scores for processing speed. Equal learning rates among the three groups suggest that unintentional learning in schizophrenia and in the elderly is preserved. These findings are important for the design of rehabilitation programs for schizophrenia.

INTRODUCTION

Schizophrenia is a psychiatric disorder, characterized by positive symptoms (e.g., hallucinations and delusions), negative symptoms (e.g., avolition and reduced emotional expressivity), and severe cognitive disabilities. Since cognitive deficits in schizophrenia are significantly correlated to poor functional outcomes[94] and quality of life[95], the development of pharmacological and remediation techniques addressing these impairments could be highly beneficial to the clinical outcome.

Cognition is not a single entity but can be divided into several domains. In schizophrenia research, the areas of primary interest are processing speed, attention/vigilance, working memory, verbal learning, visual learning, executive functioning and social cognition[32]. The combination of these domains may contribute differently to the overall clinical picture of cognitive decline in schizophrenia. Experimental tasks that focus on isolating the relative influence of these specific cognitive domains are needed to specify which deficits are most pronounced in order to provide a targeted treatment.

Processing speed has been shown to be a very distinguishing and reliable factor to characterize cognitive deficits in schizophrenia[96]. This parameter reflects the speed with which different cognitive and sensorimotor functions are executed[20]. Viewed from a traditional experimental psychology perspective, processing speed can be conceived as the total sum of three different stages of information processing, namely perceptual analysis, response selection, and response execution[31,97]. Although there are several neuropsychological tests for measuring reduced processing speed, a recent meta-analysis[98] has demonstrated that a digit–symbol-coding task is the most sensitive test to apply to patients with schizophrenia. Moreover, this meta- analysis identified processing speed impairment as the largest single deficit in the cognitive abilities of schizophrenia[98,99].

Digit–symbol-coding tasks have been carried out in two different ways. In one version, the Digit–Symbol Substitution Test (DSST), symbols must be drawn under their corresponding digits according to a key of digit–symbol combinations, provided at the top of the sheet. The second version is the symbol-coding subtest of the Brief Assessment of Cognition in

Schizophrenia included in the MATRICS Final Battery[3,31]. This task does not require the drawing of symbols but rather the numerals (1–9) must be written as quickly as possible under the corresponding symbols, which are presented in rows on the response sheet. This version of the coding task has been called the Symbol–Digit Substitution Test (SDST). In the present study, as in our previous studies[20,100], we have used the SDST in order to avoid drawing unfamiliar graphic symbols, which requires a time-consuming process of motor planning.

In the measurement of processing speed using a digit–symbol coding task, at least two factors might play a considerable role. First, digit–symbol coding tasks have a strong sensorimotor component (i.e., fine motor writing skills of the symbols or the digits). A reduction in sensorimotor speed, characterized by a longer initiation and/or execution of graphic movements, might indeed contribute substantially to low coding task performance. Previous research by Morrens et al. has demonstrated that schizophrenia patients display both sensorimotor and cognitive slowing and that these two processes are unrelated to each other[100].

In addition to a possible sensorimotor component, a second possible factor, which may influence the measurement of processing speed is het effect of (implicit) learning of the specific symbol–digit combinations. Learning is a well-known impairment in schizophrenia[7,99,101,102] in addition to processing speed. Once the symbol–digit relationships are learned, it is no longer necessary to rely on visual scanning of the key on top of the administration sheet, rather working or episodic memory can be used instead for the right response. This strategy might reduce the time in finding the right response, resulting in an increased score on the test. There may be large individual differences in the speed of learning these symbol–digit relations and in their memory capacity. Similarly, Bachman et al.[103] and Joy et al.[104] proposed that a reduced cognitive processing speed in schizophrenia might be partially due to a mnemonic deficit. Other studies on this topic concluded that the contribution of memory to symbol–digit coding performance might be relatively small but relevant[104]. However, many of these previous studies have used regression- based approaches in which coding performance was correlated with additional neuropsychological tests[103]. In an older version of the Wechsler Adult Intelligence Scale (WAIS-III), the Digit– Symbol-coding test was even followed by an implicit learning

test to assess the recall of the symbol–digit relations[105]. Bachman et al. rightly argued for a complementary experimental approach in which the symbol-coding task is manipulated to determine the role that several sub-processes might play in coding tasks. However, a disadvantage of this latter approach is that changing the task might have consequences for the relative contribution of these subprocesses.

In this experimental study, the subjects' pen movements were recorded on a writing tablet under the test sheet in order to precisely measure the time taken to write each digit (writing time) as well as the preceding time necessary to decode a symbol into its corresponding digit (matching time). The task requires to write the digits as quickly as possible; therefore, the writing time provides an estimate of sensorimotor speed whereas matching time reflects the duration of the cognitive processes that are needed to find or recall the digit that corresponds to the stimulus symbol.

Because matching time and writing time were registered for every single digit, its decrease per symbol–digit combination offers an estimate of both the rate and the amount of learning within one (90s) test administration. In addition, by administering the same test on three separate days, we were able to assess the amount of long-term learning of the symbol–digit relations.

Schizophrenia has been previously hypothesized as a generalized syndrome of accelerated ageing[106]. Since the earliest descriptions by Emil Kraepelin, schizophrenia has been referred to as "dementia praecox," literally meaning "a cognitive decline in young age." Several studies have also shown that processing speed as measured by the SDST is a fundamental mediator of age-related cognitive decline[107,108]. Therefore, comparing the performance of schizophrenia patients to elderly individuals could offer secondary, but valuable information as to what extent and in which domains the cognitive decline in schizophrenia resembles age-related cognitive impairment, referred to as "mild cognitive impairment". To our knowledge, a direct comparison of performance on the SDST between schizophrenic and elderly individuals has never been conducted.

In summary, the present study was set up to investigate the relative contribution of learning and sensorimotor speed during SDST performance. Patients with schizophrenia, age-matched healthy controls, and elderly

volunteers were tested in order to assess different effects of these factors in the different groups. The first hypothesis was that processing speed would be lower in schizophrenia patients compared with age-matched healthy controls. In addition, it was expected that this study would replicate the well-known findings of reduced writing speed in schizophrenia. As visual and verbal learning and memory have been frequently found to be impaired in patients with schizophrenia[31], it was further hypothesized that the rate and amount of the learning of the symbol–digit relations would be reduced in the schizophrenia patients. The comparison of schizophrenic and elderly individuals was exploratory.

MATERIALS AND METHODS

Study design

Our study group consisted of 30 patients with stable schizophrenia, 30 age- and sex-matched control participants, and 30 sex-matched elderly volunteers (aged 65–85 years). The SDST was administered three times on three separate assessment days.

The test was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices, applicable regulatory requirements, and in compliance with the study protocol. This study was held at the University Psychiatric Hospital Duffel, Belgium, and the study protocol was reviewed and approved by the institute's Ethics Committee.

Participants

The previously mentioned test subjects were recruited from the local community. Prior to the start of the study, they all provided a written informed consent and their eligibility for this study was assessed according to some inclusion and exclusion criteria. The inclusion criteria for patients were: (1) being an in- or outpatient with schizophrenia or schizoaffective disorder (DSM-IV), (2) having a known history of schizophrenia for at least 12 months confirmed by the treating psychiatrist and (3) receiving stable antipsychotic drug therapy (maximally 2) for at least 6 weeks prior to screening. The inclusion criteria for all participants were: (1) being a man or woman between 18 and 55 years old (schizophrenia patients and young controls) or between 65 and 85 years old (elderly volunteers) and (2) being medically stable. The exclusion criteria applicable to all participants were (1) having a DSM-IV diagnosis of substance dependence or abuse within 3 months prior to screening evaluation (only caffeine dependence was not exclusionary), (2) use of benzodiazepines, tricyclic antidepressants, or anticholinergic medication, (3) having a positive urine screen for drug abuse or a positive alcohol breath test at screening and on one of the test days, (4) having a clinically significant acute illness within 7 days prior to screening. Since the use of alcohol and drugs could potentially influence the study data, an alcohol breath test and a urine drug screen were performed before the start of each assessment day.

Symbol-digit substitution test

The task was performed on two subsequent sessions (day 1 and day 2) and a third time (day 7). The SDST was the first task to be performed on every assessment day in a larger series of cognitive tests, which will be published elsewhere. In order to avoid influences of the circadian rhythm, also the time on which the test was administered was comparable for each subject. The coding task required to translate 9 different symbols into the digits 1–9 on five rows each consisting of 25 symbols, according to a key of symbol–digit pairs, which was presented on top of the task sheet. The same symbol–digit combinations were repeated over the three session days. In line with our previous studies[10,20,100], we used the reversed version of the classical DSST where the digits had to be written under the symbols, denoted by SDST. We chose for this design in order to exclude the complication of processes of motor planning by the drawing of complex graphic symbols on SDST performance. The nine different symbols were presented in blocks. The sequence in which they were presented within each block was randomized.

A quiet environment was chosen to perform this task. The participants were asked to decode the list of symbols one by one as fast as possible within a preset 90s limit, based on the key above, writing the correct digit under the corresponding symbol on a sheet of paper placed on a digitizing tablet (WACOM1218RE) with a special pressure-sensitive normal-looking ballpoint pen. Pen position was recorded at 200 Hz and with 0.2mm spatial accuracy and stored on a standard personal computer. The signals were subsequently filtered by means of a fast-Fourier analysis. These digitized recordings allowed the computation of separate matching- and writing times.

Identical instructions were repeated each day, before the start of the task. Feedback was not provided at the end of the session. All subjects had to undergo a practice trial on the first assessment day, consisting of filling in the last 10 symbol–digit pairs, allowing them to get familiar with the experiment.

Statistical analysis

All data were analyzed using a general linear model (GLM) repeated measures in IBM®SPSS® Version 22. First, we analyzed the Session effect (long-term learning) with Group (three levels) as the between-subjects variable and Session (or days, with three levels) as the within-subjects variable. A second analysis used Block (five levels, short-term learning) and Session (three levels) as the within-subject variables and Group (three levels) as the between-subject variable. We performed separate analyses for (1) the number of correct digits, (2) the mean matching time per digit, and (3) the mean writing time per digit. Wilk's Lambda was used in the tests of the within-variable effects. A p-value of <0.05 was considered significant.

The number of blocks that could be analyzed depended on the lowest test score (number correct) obtained by the participants. Matching and writing time were analyzed over five blocks (i.e., number correct is 45 or higher). This score was gained in all three sessions by 25 patients with schizophrenia, 28 elderly volunteers, and 28 controls. Including more participants in the analysis would result in too many missing values in the fourth and fifth block whereas analyzing more than five blocks would result in an unrepresentative low number of participants. Per block, the median matching time and median writing time were calculated. Only correct digits were analyzed, and the first digit of a row was eliminated from analysis because the transport distance to this location was more than 20 cm instead of the normal 0.8 cm. In session 3, the data of one patient were missing.

RESULTS

The main objective of the present study was to evaluate the role of learning processes during SDST performance. Firstly, demographics will be described (see Demographics) followed by the general test scores on the SDST [see Test score (Number of correct digits)]. Matching time and writing time of test scores were separately calculated (see Long-Term Learning Matching and Writing Time and Short-Term Matching and Writing Time Over Blocks Per session), and the added effects of long-term learning (section Long-Term Learning Matching and Writing Time) and short-term learning (see Short-Term Learning Matching and Writing Time Over Blocks Per session) were assessed. In a final section (see Estimating the Effect of Short-Term Learning on the SDST Score), the relative contribution of short-term learning on the overall SDST score was calculated.

Demographics

The demographic features of the three study groups are shown in Table 1. All patients used antipsychotic medication at the time of testing. Sixteen schizophrenia patients were using more than one antipsychotic drug. The distribution of the different antipsychotic drugs and range of daily doses are summarized elsewhere[68]. Seven young controls, two schizophrenia patients, and no elderly individuals were left-handed. A GLM repeated measures analysis was conducted on the performance of the SDST (number correct) for the young control group with “Session” as within- subject variable and “Handedness” as between-subject variable. “Handedness” did not have a significant influence on the overall test score. The schizophrenia group had a lower mean premorbid IQ, as measured by the Adult Reading Test/ART (Dutch version: Nederlandse Leestest voor Volwassenen/NLV), than the control group ($t = 3.96$, $p = 0.0002$) and the elderly group ($t = 4.71$, $p < 0.0001$).

Table 1: Demographics

		Schizophrenia	Elderly	Control
n		30	30	30
AGE	Mean (SD)	36.43 (7.83)	69.33 (3.89)	36.77 (8.55)
	Range	23-53	65-79	18-52
IQ (ART)	Mean (SD)	101.3 (10.30)	111.7 (6.43)	110.1 (6.39)
	Range	66-115	100-124	98-130
SEX	male: female	2:1	2:1	2:1
RACE	Asian	0	0	1
	Maghreb	1	0	0
	White	29	30	29

Test score (number of correct digits)

The mean number of correct digits per session is displayed in Figure 1 for each group. This figure clearly shows an increase in task performance (long-term learning effect) over the three sessions, which was significant [$F(2,85) = 36.21$, $p < 0.001$]. This learning effect was about equal in the three groups (Session*Group interaction $p = 0.119$). On average, the three groups differed significantly in their over-all score [$F(2,86) = 21.69$, $p < 0.001$]. Both schizophrenia patients and the elderly volunteers achieved a lower test score than the controls ($p < 0.001$). Figure 1 gives the impression that the schizophrenia group performed even worse than the elderly, but the difference between these groups was not significant ($p = 0.07$) but this was only true during the first session ($p = 0.028$). After incorporating IQ as a covariate in the analysis, the group difference between schizophrenia patients and controls remained significant [$F(1,56)=23.61$, $p < 0.0001$], but the difference between schizophrenia and the elderly on session 1 was reduced to non-significance [$F(1,57)=0.60$, $p = 0.443$].

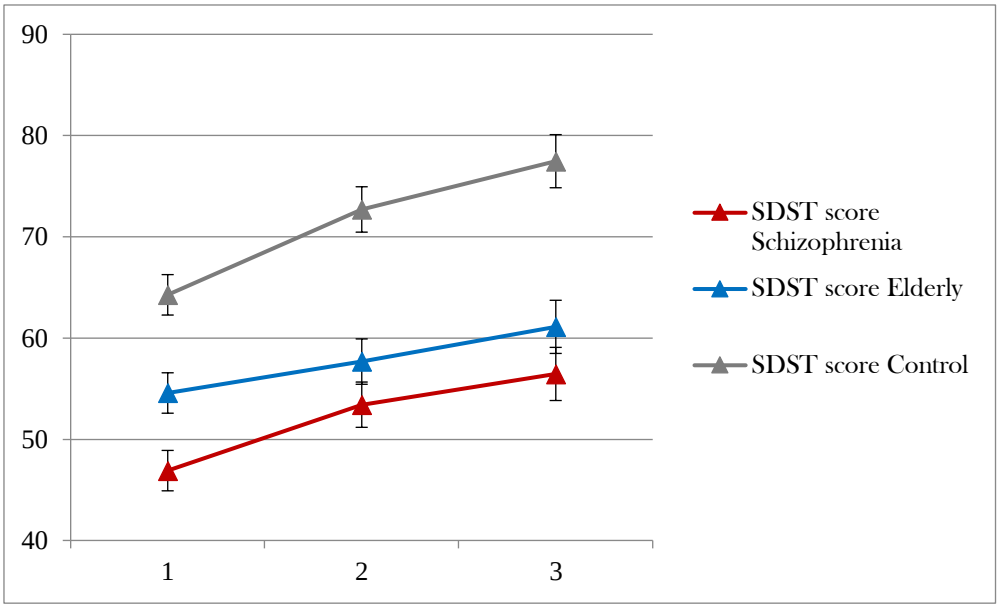

Figure 1: Means (and SE) of the number of correct digits per session for schizophrenia patients (S), elderly volunteers (E) and young controls (C).

Long term learning matching and writing time

Mean matching time per digit and mean writing time per digit are presented in Figure 2 for each session and each group.

Mean matching time per session - Figure 2 demonstrates that the matching times mirror the SDST performance of Figure 1. A clear learning effect over sessions was found [F (2,85) =32.46, p <0.0001], which was equal for the three groups [Group*Session interaction: F (2,85) =1.49, p =0.206]. Averaged over all sessions, the matching times in each group differed significantly from each other [F (2,86) =13.39, p <0.001]. Planned contrasts show a significant difference between patients and controls (p <0.0001), between patients and elderly (p =0.002 after Bonferroni correction), but not between the elderly and the controls (p =0.167). IQ (ART) as a covariate was significant [F (1,85) =14.50, p =0.0003]. IQ did not influence the difference between patients and controls (p =0.001) but reduced the difference between elderly and schizophrenic participants to non-significance (p =0.282).

Mean writing time per session - The writing times as displayed in Figure 2 do not show much variation over the test sessions, and the session effect was not significant [F (2,85) =1.36, p =0.262]. Therefore, we may conclude that there was no evident learning in the writing of the digits. Neither was the Group*Session interaction significant [F (4,170) =0.45, p =0.771]. On the other hand, the differences between the groups were relatively large and significant [F (2,86) =26.37, p <0.0001]. The elderly wrote significantly slower than the patients (p =0.0003) and the patients wrote significantly slower than the controls (p =0.001).

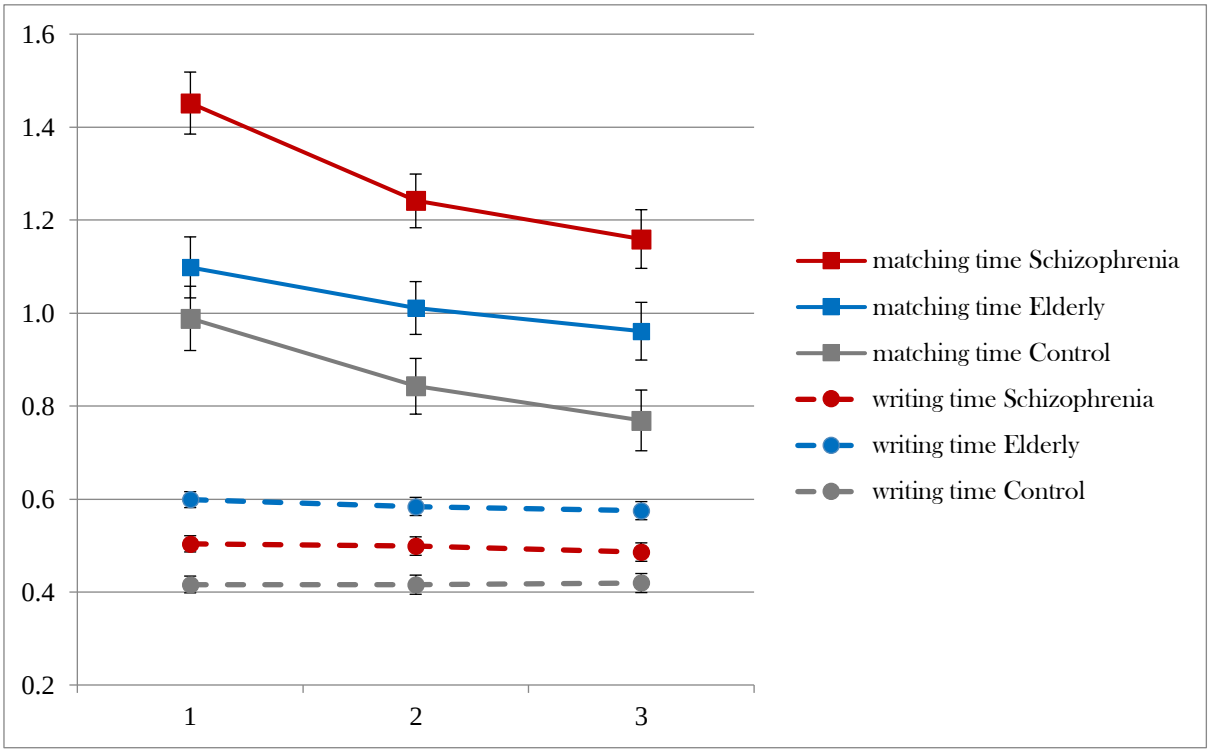

Figure 2: Means and SE for matching and writing time per session for schizophrenia patients (S), elderly volunteers (E) and young controls (C)

Short-term learning matching and writing times (over blocks per session)

Within-session learning effects are shown in Figure 3, which displays mean matching and writing times per digit for each of the five blocks in the three sessions.

Mean matching time per block - Figure 3 illustrates a decrease in matching time over the blocks and over sessions. A GLM repeated measures analysis confirmed that matching time decreased significantly over blocks [short-term learning; $F(4,75) = 21.66$, $p < 0.0001$] and over sessions [long-term learning; $F(4,75) = 21.66$, $p < 0.0001$]. The decrease over blocks was about equal in the three sessions [$F(8,71) = 1.74$, $p = 0.105$] and seemed to be similar in the three groups [$F(8,150) = 1.709$, $p = 0.101$], but the highest order interaction (session*block*group) was significant [$F(16,142) = 1.79$, $p = 0.038$]. Therefore, separate analyses were run per session. In these analyses, only the linear block effect was tested (i.e., a linear decrement of matching time over blocks; see the dashed lines in Figure 3). In session 1, this linear block effect was significant [$F(1,78) = 31.04$, $p < 0.0001$], denoting a significant short-term learning effect (decrement over blocks), but this learning effect was similar for the three groups [block*group Linear: $F(2,78) = 0.03$, $p = 0.597$]. In the second and third sessions, more participants reached the minimum criterion of 45 correct digits, but the analyses of the Linear trends yielded similar results [session 2: block: $F(1,83) = 29.08$, $p < 0.0001$; block*group Linear: $F(2,83) = 2.75$, $p = 0.070$; session 3: block: $F(1,83) = 25.20$, $p < 0.0001$; block*group Linear: $F(2,83) = 1.95$, $p = 0.148$]. Therefore, these results suggest that the rate and amount of short-term learning (repetition over blocks) was similar in the three sessions and about equal among the three groups.

Mean writing time per block - Writing time in Figure 3 shows that there is not much variation over blocks and sessions. The only noteworthy result is the relatively long writing time of the elderly participants. An analysis of writing time with session and block as the within-subject variables and group as the between-subject variable showed that the effect of session was not significant, but the block effect was [$F(4,75) = 5.60$, $p = 0.0003$]. None of the interactions were significant either. In the first session, the linear block effect was not significant ($p = 0.216$), but the linear block*group inter-

action was significant [F (2,78) =3.55, p =0.033]. This is probably due to a slight decrement of writing time by the elderly but not by the other two groups. In the second and third session, the linear block effect and the linear block*group interactions were not significant, indicating that writing time remained stable in these sessions.

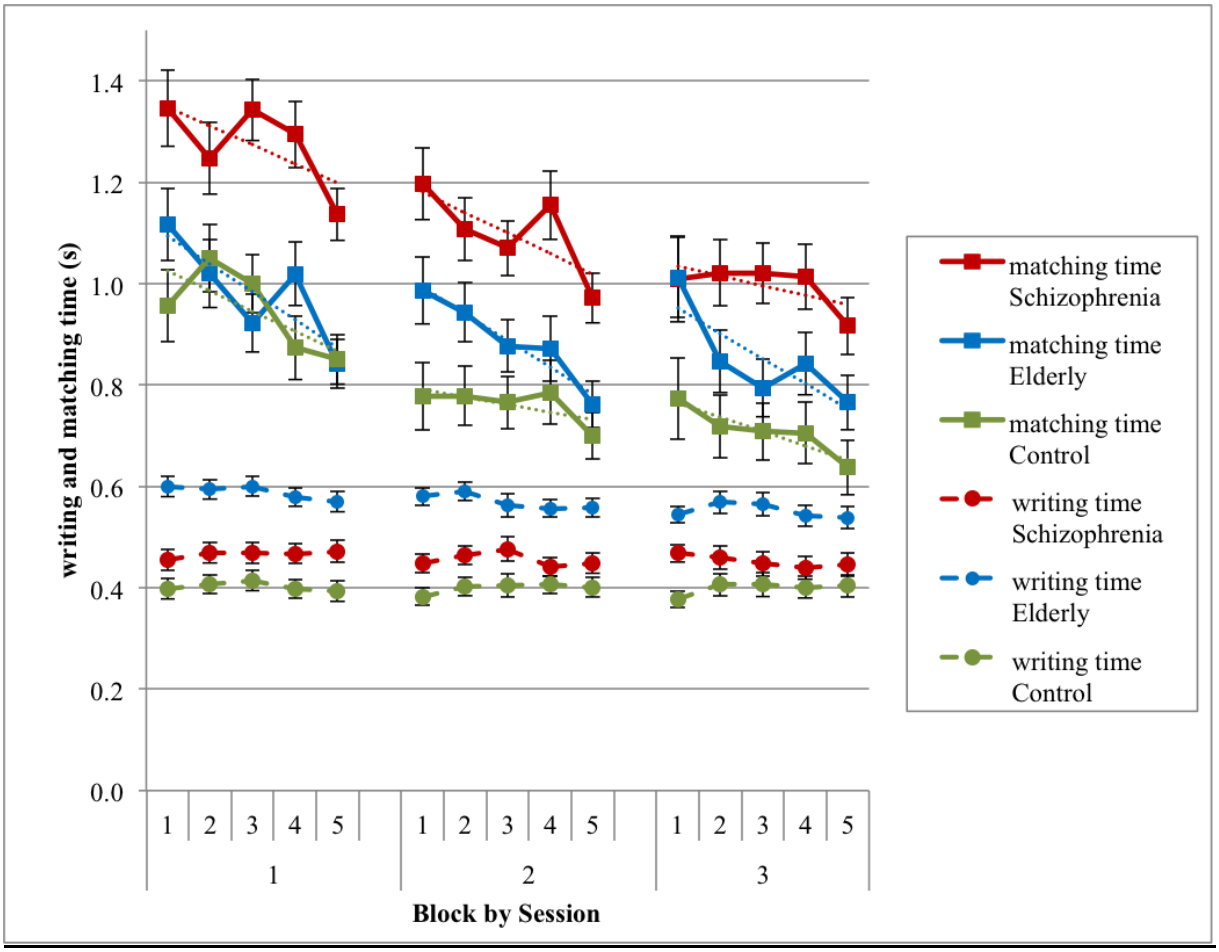

Figure 3: Means and SE for writing and matching time per block and per session for schizophrenia patients (S), elderly volunteers (E) and young controls (C).

Estimating the effect of short-term learning on the SDST score

To estimate the contribution of the linear decrease in matching time to the SDST score, we estimated the score that would have been obtained if the matching time (mt) and writing time (wt) of the first block (i.e., mt1 and wt1) had been maintained over all blocks in the 90 s of the test [i.e., estimated score = 90/(mt1+wt1)]. We did the same for block five. The result of this estimation for session 1, i.e., for the standard test administration, was that the score of all participants had improved, more specifically from 50 to 56 for patients with schizophrenia, from 52 to 64 for the elderly and from 66 to 72 for the controls. These are increases of 12, 23, and 9%, respectively. It should, however, be stipulated that not all participants showed a decrease in matching time over blocks. Slopes ranged considerably, with the largest range found in the group of schizophrenia patients (from +78 ms/block to −301 ms/block; mean=−37 ms/block) compared to the ranges of the young controls (from+50 ms/block to −284 ms/block; mean=−39 ms/block) and the elderly volunteers (from+38 ms/block to −236 ms/block; mean=−55 ms/block).

DISCUSSION

Summary of results

The main purpose of this study was to assess to what extent difference in symbol–digit learning influences the performance on the SDST. The present findings demonstrate that the repetition of symbol–digit pairs during one test administration (short-term learning), and the repetition of the same test over several days (long-term learning), resulted in significant decreases of matching time. Interestingly, these learning effects on matching time were about equal for patients, age-matched controls, and elderly participants, while the overall test score differed among the groups. In contrast, writing time, reflecting sensorimotor speed, remained about equal over symbol–digit repetitions. Patients had the lowest overall score and the longest matching time; however, the difference between patients with schizophrenia and elderly was no longer significant after controlling for the lower IQ of the patients.

Sensorimotor speed had a smaller impact on the overall test performance, but there were significant differences between the three groups with the elderly clearly being the slowest writers.

Rationale for the chosen methodological approach

In an experimental approach of the coding task, like the one adopted by Bachman et al. (15), single symbol–digit pairs are presented trial by trial and on each trial the participant must quickly decide whether the presented combination is identical to one of the digit–symbol pairs in the reference code that is simultaneously presented on the PC screen. In the more common paper-and- pencil version of the task, the participant can work at his own pace and might (learn to) combine the activities of both writing a digit and searching for the next digit that matches the next symbol in parallel. We opted to incorporate an experimental approach into the continuous paper-and-pencil version, because recording of the pen movements enables the separate measurement of reaction time (now denoted by “matching” time) and response execution time (“writing” time). In addition, to allow an unbiased estimate of learning we adapted the presentation of the symbols that had to be coded. In standard symbol-coding tests, not all nine symbols are already shown in the first block, but

they are introduced gradually to promote the learning of the symbol–digit relations. For our SDST version, however, we preferred to present all nine symbols with the same frequency right from the start. As a result, a repetition of the same symbol–digit pair was separated by an average of eight other pairs. Yet, considerable learning did occur as evidenced by the linear decrease in matching time over nine-symbol blocks.

Influence of learning processes on the SDST score

Comparing the size of the learning effects with the SDST scores showed that the influence of learning processes on the SDST score in schizophrenia, the elderly and younger controls varies greatly from person to person. The average learning effects found in the present study of about 12% in the schizophrenia group and 23% in the elderly can be classified as rather substantial. This is in line with the conclusions drawn by Bachman et al.[103] and Joy[104]. It deviates from Salthouse's[109] interpretation in which memory factors are assigned only "a very small role in contributing to the age decline in digit–symbol performance."

Identification of learning processes

Repetition of the same task results in learning. Therefore, the decrease in matching time over blocks within one session as well as over more sessions must be the result of a learning process. But what exactly is learned during the repetitions of symbol– digit pairs is less clear. Two critical processes are known to be involved in the search for the matching digit: visual scanning[110] and relational memory[104]. First, visual scanning, refers to the early detection and identification of visual stimuli, either alone or in the presence of competing stimuli. The role of visual scanning is emphasized when participants consult the code key frequently during test administration. Possibly, visual scanning might improve by learning the position of the symbols in the key. Second, relational memory, refers in this context to the memory for associations in the SDST[3,101]. Learning the relations between symbols and digits will reduce the necessity for searching, which automatically results in a decreased matching time. A third process that might be involved in the reduction of matching time over repetitions is a change in the strategy to perform the task. An impairment in response selection[111,112], i.e., the process of mapping stimuli to specific responses and decision making could possibly cause a considerable amount

of the lower performance observed in schizophrenia. Most participants will start with performing matching and writing strictly after each other, while some participants might learn to do part of the writing and scanning in parallel. In that case, the search for the next digit has already started during the automatic writing of the current number.

Overall, various learning processes might contribute to a decreased matching time, but their relative contribution could not be deduced from the present study. To find more detailed answers, experimental changes of the task, like the manipulations tested by Bachman et al., are needed. For now, we can only conclude that these learning processes occurred unintentionally, and therefore, should be denoted by the term "implicit learning." An important outcome of this study is that the rate of this implicit learning was not significantly different among the three groups.

Sensorimotor speed

The second aim of our investigation was to evaluate the effect of differences in writing speed on the SDST score. Group differences in writing speed were highly significant but smaller than the group differences in matching time. Schizophrenia patients wrote significantly slower than same-aged controls and the elderly had the lowest writing speed. The effects of reduced writing speed in schizophrenia and the elderly on the total test score were smaller than the estimated effects of learning (for schizophrenia, learning+12%, writing speed+4%; for the elderly, learning+23%, writing speed+13%).This leads us to the conclusion that the usual determination of the symbol-coding test score results in underestimation of the speed of information processing, particularly for the elderly.

Schizophrenia and the elderly compared

Healthy elderly persons were included in this study in order to compare the reduction in the speed of information processing of the schizophrenia patients with normal, age-related cognitive decline. By correcting for sensorimotor speed and only taking the matching time as an index of processing speed, patients performed worse compared to the elderly volunteers (aged 65– 85 years). However, when an estimate of premorbid intelligence (the Adult Reading Test) was considered, the differences in

matching time were no longer statistically significant, while the difference between patients and same-aged controls remained significant. Although the similarity between the elderly and the patients with schizophrenia on matching time is striking, we cannot deduce from these data whether schizophrenia should be seen as "dementia praecox." In addition, it should be acknowledged that the elderly had a small but significantly lower sensorimotor speed. Only sensorimotor speed differentiated all three groups.

Study limitations

Due to patient selection, a bias might exist since only patients who were able to complete the test batteries were included in this study. The neurocognitive abilities of the selected patients may therefore be higher than the group of schizophrenia at large. Thus, the results of this study may not be generalized to the whole population of patients with schizophrenia. However, the mean SANS score for schizophrenia patients of 25.7 (SD 17.39) that was measured on screening visit is comparable with the mean SANS score of 23.0 (SD 14.6) found in a large heterogeneous sample of schizophrenia patients[113]. Additionally, only 4.2% of our study sample was excluded after screening visit, suggesting that the internal validity of our study is high.

Implications for future research and clinical practice

There is a wide variation in the administration of symbol–digit coding tasks ranging from a classical pen-and-paper writing task to a purely computerized test, which simply requires pressing a button when the correct symbol–digit combination appears. These different methods may ask for different cognitive sub-processes in the total test score. As an example of this, the present study clearly showed that the time taken by the motor part of the test must be considered in interpreting symbol–digit coding test scores as measures of the speed of information processing.

The large variation between individual participants in the rate of short-term learning could argue for the need of additional memory test information to assess to what extent the (possibly) low SDST score has been the result of a learning failure. Some healthy volunteers mentioned spontaneously at the end of a session that they had remembered the

symbol–digit combinations but we did not give a questionnaire to draw further conclusions toward awareness differences among the groups. Therefore, we suggest that the addition of a self-rater or observer-rater questionnaire might be valuable to address the possibility of different explicit and implicit learning strategies.

Although schizophrenia is often characterized by a reduced speed of information processing, the present study showed a similarity with the control group and the elderly as far as the rate and amount of both short-term and long-term implicit learning was involved. This was found despite the general finding of impaired working memory and a lower rate of explicit verbal and visual learning in schizophrenia. Because we speculate that improving processing speed may be predictive for the functional outcome, we recommend that more attention should be paid to implicit learning in future schizophrenia research and in the design of specific rehabilitation programs.

CONCLUSION

We can conclude that the two factors that were studied both influenced the estimation of processing speed with the Symbol–Digit Substitution Test. The average effect of learning the symbol–digit relation on the SDST score was substantial and the large individual differences in the amount of learning deserves more attention. The effects of sensorimotor speed on the total test score were shown to be smaller than the learning effects but cannot be neglected because they lead to an underestimation of the speed of information processing, particularly for the elderly. The finding of equal unintentional learning effects in patients, their age-matched controls and elderly participants lead us to the conclusion that implicit learning might be preserved in schizophrenia. This finding has important consequences for the design of specific rehabilitation programs for schizophrenia patients.

CHAPTER V - SEQUENCE LEARNING

Implicit motor sequence learning in schizophrenia and in old age: reduced performance only in the third session

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Implicit motor sequence learning in schizophrenia and in old age: reduced performance only in the third session

ABSTRACT

Although there still is conflicting evidence whether schizophrenia is a neurodegenerative disease, cognitive changes in schizophrenia resemble those observed during normal ageing. In contrast to extensively demonstrated deficits in explicit learning, it remains unclear whether implicit sequence learning is impaired in schizophrenia and normal ageing.

Implicit sequence learning was investigated using a computerized drawing task, the 'implicit pattern learning task' (IPLT) in 30 stable patients with schizophrenia, 30 age-matched controls and 30 elderly subjects on two consecutive days and after 1 week (sessions 1, 2 and 3). Fixed sequence trials were intermixed with random trials, and sequence learning was assessed by subtraction of the response time in fixed sequence trials from random trials. Separate analyses of response times and movement accuracy (i.e., directional errors) were performed. Explicit sequence knowledge was assessed using three different awareness tasks.

All groups learned equally during sessions 1 and 2. In session 3, control subjects showed significantly larger learning scores than patients with schizophrenia ($p=.012$) and elderly subjects ($p= .021$). This group difference is mainly expressed in movement time and directional errors. Patients with schizophrenia demonstrated less subjective sequence awareness, and both patients with schizophrenia and elderly subjects had less explicit sequence recall. Explicit recall was positively correlated with task performance in all groups. After a short 24 h interval, all subjects showed similar improvements in implicit sequence learning. However, no benefit of prior task exposure 1 week later was observed in patients with schizophrenia and elderly subjects compared to controls.

As patients with schizophrenia and elderly both display less explicit sequence recall, the control group superiority after 1 week could be explained by an explicit learning component. The few patients with schizophrenia and elderly subjects who had some sequence recall could

possibly utilize this explicit knowledge to improve their task performance but did this by distinct mechanisms.

INTRODUCTION

The functional outcome of schizophrenia is substantially correlated with the severity of the cognitive symptoms[114]. The fast and progressive cognitive decline led initially to the conceptualization of schizophrenia as a disorder of chronic brain deterioration (Kraepelin 1971). Although the neurodegenerative nature of schizophrenia is currently under debate, there is evidence supporting the hypothesis that schizophrenia is associated with accelerated ageing at a genetic and neuroanatomical level[115]. On a clinical level, both patients with schizophrenia and normal ageing subjects show a decline in cognitive functioning. However, patients with schizophrenia experience the greatest cognitive decline over a shorter period (mainly during the premorbid and prodromal stage of the illness)[116] compared to normal ageing-associated changes. For this reason, Kirkpatrick et al.[52] argued that the early stage of schizophrenia can be considered as a period of 'compressed ageing.' Importantly, there is a strong overlap between the cognitive domains that are affected in schizophrenia and those that are also vulnerable to decline in normal ageing with processing speed, high-load information processing and explicit learning being the cognitive domains that are most consistently demonstrated to be affected[117]. Even though both groups seem to display similar deficits on identical neurocognitive tasks, to our knowledge, the performance between healthy elderly volunteers and patients with schizophrenia has never been directly compared on the same tasks.

While deficits in explicit learning have been extensively demonstrated[44,118], the literature is still inconclusive whether implicit learning is impaired in both schizophrenia[43,46] and normal ageing[119,120].

Implicit learning refers to the automatic and unconscious learning of information in contrast to explicit learning which involves the deliberate purpose to learn and requires conscious awareness[101]. Implicit learning is a complex cognitive domain covering different learning paradigms[121] which can be separately investigated by distinct neuropsychological tasks. While

probabilistic classification, rotor pursuit, artificial grammar learning and word-stem completion tasks have been typically found to be preserved in schizophrenia[101,122], implicit sequence learning (ISL), which refers to unconscious incremental acquisition of sequential information, has been reported to be impaired[45,46]. ISL involves primarily the dorsolateral striatum, the primary (pre)motor cortex and cerebellum[123,124] and is unrelated and fundamentally different from explicit sequence learning, which involves the anterior striatum and the prefrontal cortex[125].

The serial reaction time task (SRTT)[126] has proven to be a relevant instrument to study motor sequence learning in many human populations. In the implicit SRTT version, unknown to the participants, a fixed sequence of visual targets is usually presented repeatedly on a computer screen. Participants are instructed to react as fast as possible to these targets by pressing on a spatially corresponding button on a keyboard. Two main implicit learning components contribute to test results, namely sequence-specific learning and task-specific learning. Participants learn the sequence based upon the order in which the fixed targets appear on the screen (a form of visuospatial learning) and upon the order in which associated movements (such as key presses) are made (a form of sensorimotor learning). These two sequence learning mechanisms derive from distinct brain areas and circuits[127]. Task-specific learning (a form of procedural learning) encompasses all task-related information such as feedback signals, timing and location of stimulus presentation, or the position of the hand and fingers.

Up until to date, it remains unclear whether ISL as measured by the SRTT is impaired in schizophrenia[43,128] and during ageing[119,120,129]. These inconsistent findings may be explained by methodological limitations in previous SRTT studies in both populations.

Firstly, studies used small numbers of sequence repetitions (5–10 fixed sequence repetitions and only one session)[130]. However, it has been shown that the amount of online ISL depends on the number of sequence repetitions per session[131]. In addition, as few longitudinal studies are available, there is no clear understanding about retention and offline consolidation effects[132].

Secondly, most SRTT studies use little visuospatial variation in their tasks and might be too simple to detect visuospatial deficits. However, it has also been shown that there are specific visuospatial deficits in schizophrenia[133–135] and ageing[136] that influence implicit learning. For example, studies using non-visuospatial versions of the SRTT in schizophrenia found only accuracy (i.e., error-related) deficits, whereas a visuospatial version demonstrated larger impairments on both accuracy and response times[125]. Using the implicit pattern learning task (IPLT), a task with more visuospatial demands, learning deficits which were not detected by the SRTT were found in patients with mild cognitive impairment, Parkinson's disease[137] and Korsakoff's syndrome[138]; however, this task has not been used in schizophrenia.

Finally, explicit learning is well known to be impaired in schizophrenia and normal ageing, but its presence in an implicit learning task cannot be excluded[139].

In order to further investigate implicit learning in schizophrenia and elderly, it is essential to overcome these methodological limitations. This paper is part of a larger study that aims to compare the performance of patients with schizophrenia, elderly volunteers and healthy controls on a battery of different explicit and implicit psychomotor learning tasks.

The aim of the current study is to understand better whether implicit sequence learning, a skill that is indispensable in performing elementary activities such as tying shoes, is impaired in patients with schizophrenia and healthy ageing. Given the arguments for a visuospatial deficit in schizophrenia and ageing, the IPLT was used, in which pen movements toward a larger number of possible targets are recorded on a digital writing tablet. Multiple test repetitions over several days allowed a detection of possible learning deficits on later learning phases. The hypothesis of the study was that patients with schizophrenia and older subjects would show less ISL improvement across sessions than controls since it has been demonstrated that both groups display deficits in motor sequence memory consolidation[57,129]. Lastly, the presence and role of an explicit learning component was explored using three different awareness tasks, which were compared with each other and related to the task performance: a non-suggestive oral questionnaire, a sequence recognition task and an explicit

recall task. It was expected that both patients with schizophrenia and elderly would demonstrate explicit learning deficits[44,118].

METHODS

Participants

Our study group consisted of 30 stably treated patients with schizophrenia (aged 18–55 years) who had not experienced a psychotic relapse in the past 2 months, 30 age- and gender-matched control participants, and 30 gender-matched elderly volunteers (aged 65–85 years). The patients were recruited from psychiatric hospitals in the area of Antwerp, Belgium and the healthy controls were recruited from the local community. All candidates provided a written informed consent. Participants receiving treatment with benzodiazepines and anticholinergics (including tricyclic antidepressant drugs) were excluded from participating in the study because of their documented negative effects on cognition. The inclusion and exclusion criteria for the three groups are described in detail in our previously published papers where the same groups of participants were studied[63,68]. The test was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices, applicable regulatory requirements, and in compliance with the study protocol. This study was conducted at the University Psychiatric Hospital Duffel, Belgium, and the study protocol was reviewed and approved by the institute's Ethics Committee. The study is registered at ClinicalTrials.gov: NCT01788436.

Implicit pattern learning task (IPLT)

Participants were seated in front of a laptop computer and performed the IPLT writing task on a sheet of plastic that was fixed on a digitizing (WACOM) writing tablet. In order to control the cursor movements to different targets on the computer screen, subjects used a normal-looking, non-inking pen to move across the plastic sheet. The position of the pen tip was recorded on and up to 5 mm above the tablet. Sixteen 10-mm-diameter target circles were continuously displayed on the computer screen, positioned in a rhombus of four-by-four targets on equal distances from each other (see Fig. 1).

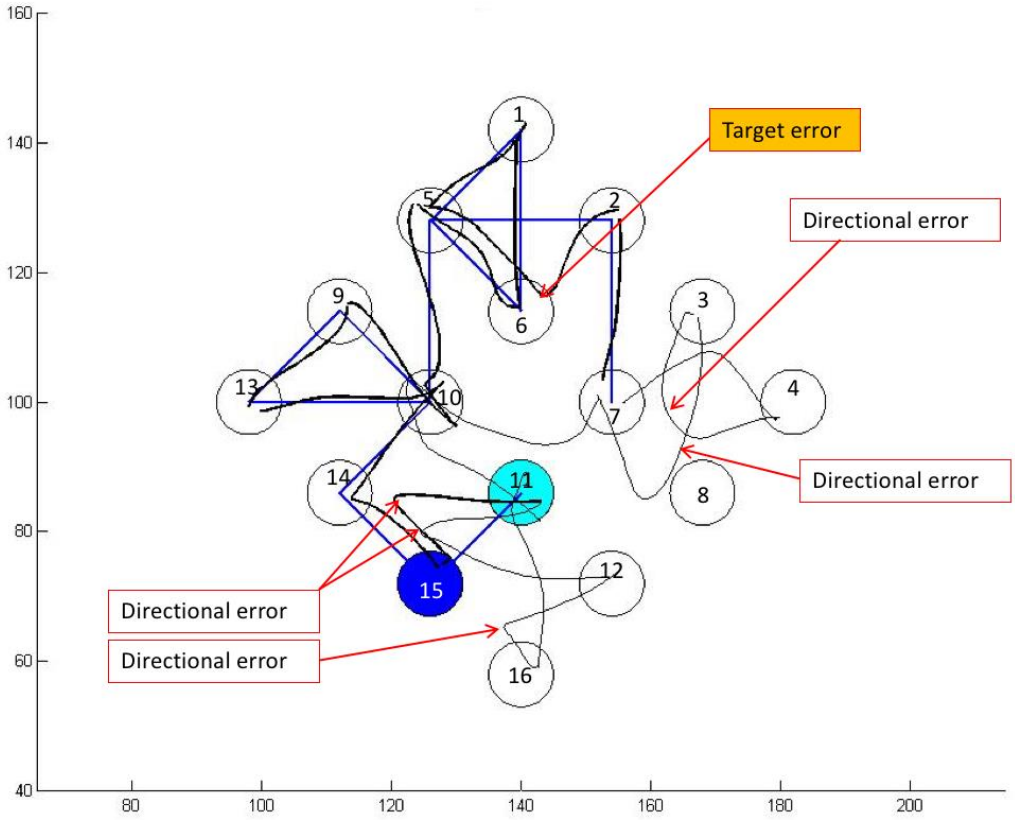

Figure 1. The target display on the computer screen during the IPLT. Turquoise circle: starting position, i.e., the previous target after being hit by the cursor. Dark blue target: the next target. Dark blue trajectory: the trajectory of the twelve consecutive fixed sequence targets starting from target 11: 15, 14, 10, 13, 9, 10, 5, 6, 1, 5, 2, and 7. Black bold trajectory: an example of pen movements on the fixed sequence targets. Black trajectory: possible pen movements on eight random targets. A target error is shown on the pen trajectory on fixed trial 6 and five movement errors in which the movement started in the wrong direction (directional errors, DE) are marked. The display seen by the participants consisted solely of the turquoise pen cursor, the sixteen circles (without the numbers), the turquoise starting position and one target circle being filled dark blue.

Each trial consisted of one target turning dark blue. Participants were instructed to move the cursor (a turquoise dot with 4 mm diameter) toward the dark blue target as quickly as possible by moving the non-inking pen on the digitizing tablet. The cursor had to be held inside that target circle for 100 ms. A correct hit (and stay of 100 ms) of the target circle by the cursor was indicated by a beep and a color change of that target circle to turquoise. From the moment the beep sounded, there was a short intertrial interval

lasting for 100–108 ms, which was needed to write the data of the previous trial away. After this, the next trial started with a new, adjacent target turning dark blue. The turquoise starting position remained visible until the dark blue target was reached. The trials were presented either in learning blocks, consisting of repetitions of a fixed 12-target sequence, or in pseudo-random blocks, consisting of eight random targets which did not contain a fixed sequence. The total duration of one IPLT session took on average 15 min.

The IPLT task was assessed in three sessions, conducted on two consecutive days (sessions 1 and 2) and 7 days later (session 3). In session 1, a first 60-trial pseudo-random block (R1) was followed by five 100-trial learning blocks (L1–L5), where the eight random targets followed by the 12-target fixed sequence were repeated five times. The five learning blocks were followed by a seventh pseudo-random block (R2) of 60 trials at the end of the session. Sessions 2 and 3 were largely similar to session 1 but consisted of only three learning blocks (L1–L3) instead of the original five. In between the blocks, participants were given a short self-timed break of about 20 s to reduce fatigue. All participants were examined individually.

On each session, the IPLT was performed as the third task during a larger 120-min neuropsychological test battery, after having performed a symbol digit substitution task, of which the results have been published elsewhere[63]. Before every IPLT session, a practice exercise was performed in order to get familiar with the use of a digital writing tablet, the non-inking pen and the coordination between pen movements and cursor movements on the computer screen.

Awareness tasks

The participants were not informed about the repeated sequence. Yet, by debriefing following each IPLT assessment a subjective awareness test was performed. After this debriefing on session 3, participants were informed about the fixed sequence, after which two additional more objective tests, one recognition test and one recall test, were performed.

Subjective awareness test

After each IPLT session, participants were asked if they had noticed anything with respect to the task to probe whether they had become aware

about the tasks' fixed sequence. Because the participants needed to remain naïve about the fixed sequence until the end of the session 3, this question was asked in a sensitive, non-suggestive fashion. A degree of explicit awareness was scored when participants were able to verbalize that there seemed to be a repeating pattern in the task or found the middle (learning) blocks went smoother.

Recognition test

Four blocks each consisting of twenty trials were performed with the third block containing the fixed sequence and the other three blocks being entirely different from the fixed sequence. The participant was asked to estimate how likely it was that this sequence appeared during the IPLT by scoring each block on a scale of 0–100 % with 0 % meaning absolute certainty that the sequence did not appear in the IPLT and 100 % indicating that the subject was entirely certain that the presented sequence was identical to the fixed sequence in the IPLT.

Recall test

Participants were asked to try to actively regenerate the pattern on two identical test blocks, consisting of the twelve sequence targets. The next target was not signaled automatically anymore, and as soon as the right circle was hit, a beep sounded and this circle turned turquoise as in the normal IPLT, after which the next target could be searched for.

Analysis

We considered the general decrease in response time and errors across learning block L1 to L5 to depend on the combination of task- and sequence-specific learning. The difference in response time on sequence trials from random block R2 to the preceding learning block L5 or L3 was regarded as a measure of sequence learning and the decrease across random trials to be caused by task-related learning.

The averaged differences in response time between the fixed and random trials and their increase over consecutive learning blocks provide an estimate of the learning rate within one session.

The mean total response time per target (TT) was separated into the time needed to initiate a movement (mean reaction time, RT) and the time needed to cross the distance between the two circles (mean movement time, MT). The RT is measured as the time between the onset of stimulus presentation and the time at which the pen left the starting circle and crossed its 0.4-cm periphery (total diameter 3.4 cm). The MT is the time taken to cross the distance between the start-circle's periphery and the periphery of the target circle. The spatial nature of the writing task allowed an analysis of detailed pen movements in different correct and wrong directions. The increase of the number of directional errors (DEs) from L5 to R2 was used as a measurement of accuracy and enabled a detection of potential learning strategies. DEs were movements that left the starting circle at the wrong angle, i.e., deviations of >22.5° from the most optimal angle. This movement toward a wrong target in the first stage of the movement could still be corrected during the later stages of the movement, in contrast to a target error where a wrong (blank) target had been hit after making a DE.

All data were analyzed with ANOVA (GLM) repeated measures in IBM SPSS version 22. The schizophrenia group was compared with the control group, and the elderly group was compared with the same control group for the measures of significance (planned comparisons). Bonferroni post hoc analysis was used to compare the schizophrenia with the elderly group. Alpha was set at 0.05 through- out the study analyses.

RESULTS

The demographic features of the three study groups and the distribution and daily doses of the antipsychotic drugs in patients with schizophrenia are summarized elsewhere (De Picker et al. 2014). As the data of one schizophrenia patient were missing due to a computer error, the performance levels of 29 patients with schizophrenia, 30 healthy controls, and 30 elderly patients were analyzed.

To assess the effect of antipsychotic medication on the amount of ISL in patients with schizophrenia, the mean doses of antipsychotics were converted to chlorpromazine equivalents (Ceq). Six patients taking a depot variant of paliperidone, olanzapine and bromperidol were excluded as it was not possible to find reliable Ceq values for these three depot antipsychotic agents. The amount of sequence learning of the remaining 23 patients did not significantly correlate with the Ceq values (Spearman's ρ: session 1 $\rho = 0.20$; session 2 $\rho = -0.34$; session 3 $\rho = 0.07$). The median dosage (400 Ceq) and the Belgian Center for Pharmacotherapeutic Information (2016) were used to divide all 29 patients into two categories of a relatively high or a relatively low dosage. Analyses of variance (GLM) on the TT values of the random and on the fixed sequence trials did not reveal any significant difference ($p > 0.20$) between the high- and the low-dose groups in any of the three sessions.

The main outcome measure of the IPLT is the TT needed to reach a target. Group means over sessions and trial blocks within sessions are presented in Fig. 2. The figure shows two lines per group: one for the eight random targets and one for the twelve targets that were presented in a fixed sequence during the learning blocks (L1–L5) and in a random order during blocks R1 and R2.

Before analyzing the data on sequence learning, we will first describe the sensorimotor learning results as shown by the responses to random targets.

Sensorimotor learning

Figure 2 shows that in general the control group (C) was much faster than the schizophrenia (S) and the elderly (E) group. ANOVA (GLM) showed on

the TT means of the eight random targets with session (3) and block (5; only the first five blocks in session 1) as within-subject factors and group (3) as between-subject variable a significant group effect (F (2,86) =26.99, p <.0001). Contrasts of group C (423ms) with group S (531ms) and with group E (541ms) were significant (both p<.0001), whereas groups S and E were not different (p =.564).

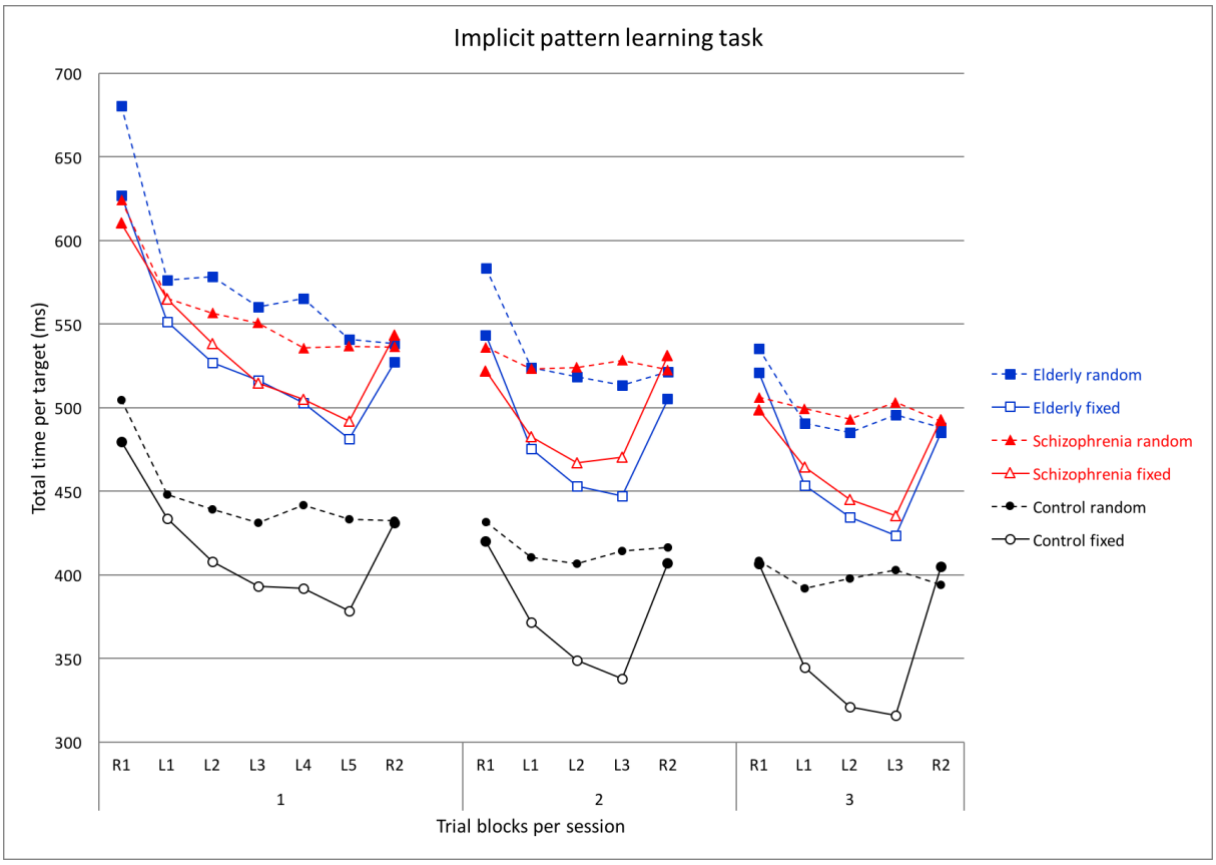

Figure 2. Mean total time to reach random (filled markers) or fixed sequence targets (open markers) per block and session for the three groups. R1 and R2 are the two Random blocks and L1, L2, L3, L4 and L5 are the five Learning blocks on session 1, 2 and 3.

ANOVA also showed considerable sensorimotor learning (TT reduction) over the three sessions (F (2,85) = 157.42, p < .0001) and over the blocks within the sessions (F (4,83) =50.88, p <.0001). In addition, group differences in sensorimotor learning rate were found, as shown in the block by group interaction (F (8,166) =5.25, p <.0001) and the session by group interaction (F(4,170) = 4.04, p = .004), while the highest order interaction (session by block by group) was not significant (p =.416). The block by

group interaction is due to a larger TT decrease from block R1 to block L3 in the elderly (C: 31ms, S: 38ms and E: 75ms; Group S vs E, block × group: $F(4,54) = 7.52$, $p < .0001$). This must have been the result of the relatively large TT of group E in the random trials of block R1, because an analysis only over blocks L1 till L3 did not produce a significant block by group interaction anymore ($F(3,55) = 2.09$, $p = .112$). Elderly persons seemed to have had much more problems with the very first trials of the task, at least in sessions 1 and 2 (see Fig. 2).

The elderly also differed in the amount of learning over sessions from the other groups. The significant session by group interaction is caused by the larger decrease in TT of the elderly (sessions 1–3: 592–532–499ms) compared to the session reductions of group S (567–527–499ms) and group C (453–416–399ms). Even when only four blocks were averaged (omitting R1) and when only groups S and E were compared, the decrease over sessions was larger in the elderly ($F(2,56) = 3.57$, $p = .035$). In Fig. 2, this is shown by the larger TT of group E compared to group S in the random targets on session 1 (particularly on blocks L2–L4) and the disappearance of this difference in sessions 2 and 3.

Sequence learning per session

The amount of sequence learning can be determined by comparing targets in a fixed sequence with a control condition in which the order of targets is random. In the present study, this was done first in the traditional way by calculating for each session the difference in mean TT of random block R2 and the preceding learning block (L5 in session 1 and L3 in sessions 2 and 3). Figure 2 shows marked increases in TT from the last learning block to the subsequent random block (R2) for all groups in all sessions. ANOVA (GLM) on session (3 levels) and block (2 levels: last learning block vs. R2) as within-subject variables and group (3 levels) as between-subject factor showed a strong effect of sequence learning (block: $F(1,86) = 313.08$, $p < .0001$). In this analysis, the effect of session was also significant ($F(2,85) = 75.99$, $p < .0001$) as well as the block by session interaction ($F(2,85) = 8.84$, $p = .0003$).

To illustrate the amount of learning in the three sessions, the differences in TT between the final random blocks and the preceding learning blocks are displayed in Fig. 3 (left panel). The figure shows that in session 1 the degree

of sequence learning was substantial (F (1,86) =159.64, p <.0001) and equal for the three groups (F (2,86) =0.28, p =.754). Session 2, compared to session 1, showed a higher degree of sequence learning in the three groups (F (1,86) =8.42, p =.005). The lack of an interaction between session (sessions 1 and 2) and group (F (2,86) =0.20, p =.816) demonstrates that this increase was about equal for the three groups. However, in session 3 the learning score of the control group improved again, while the other two groups remained on the same level as in session 2. The group by session (3 levels) interaction showed a significant linear contrast (F (2,86) =3.61, p =.031) and simple contrasts on TT differences in session 3 yielded significant group differences between the control group and the other two groups (C–S: p =.012; C–E: p =.021).

More information on this control group superiority in the third session is gained by inspection of the RT and MT components of the TT (see Fig. 3). The shortening of RT with sequence learning was substantial (F (1,86) =246.38, p <.0001), but did not improve over sessions (F (2,85) =0.24, p =.784). It was equal for the three groups (F (2,86) =1.53, p =.224) and did not show any group by session interaction (F (4,170) =1.10, p =.360). However, MT offered a different picture. Like RT, the overall reduction in MT as a result of learning the sequence was large (F (1,86) =82.56, p <.0001), but now the effects of session (F (2,85) =12.51, p <.0001) and group by session (F (4,170) =5.30, p =.0005) were significant. These effects were mainly caused by the control group. A reduction in MT can be obtained by increasing movement speed, but the main factor was probably avoiding the detours caused by starting the movement in the wrong direction. The fourth panel of Fig. 3 shows that the difference in percentage of DEs between blocks R2 and L5/L3 shows a similar picture as the differences in MT (group × session: F (4,170) =3.20, p =.015). On random trials, the percentage of DEs increased over blocks within each session from 15 to 28 % (averaged over groups; not displayed in Fig. 3). This is possibly due to an increase in the tendency to start before the proper target has been identified. On fixed sequence targets, however, DEs decrease over learning blocks (in session 2 from 21 to 18% and in session 3 from 20 to16%). When the fixed sequence turns into a random order, in the R2 blocks, large increases in percentage of DEs occur (shown in Fig. 3) which result in higher numbers of corrected trajectories with large detours from a

straight path. This effect proved to be stronger for the control group in session 3 (simple contrasts C–S: p =.015; C–E: p =.021).

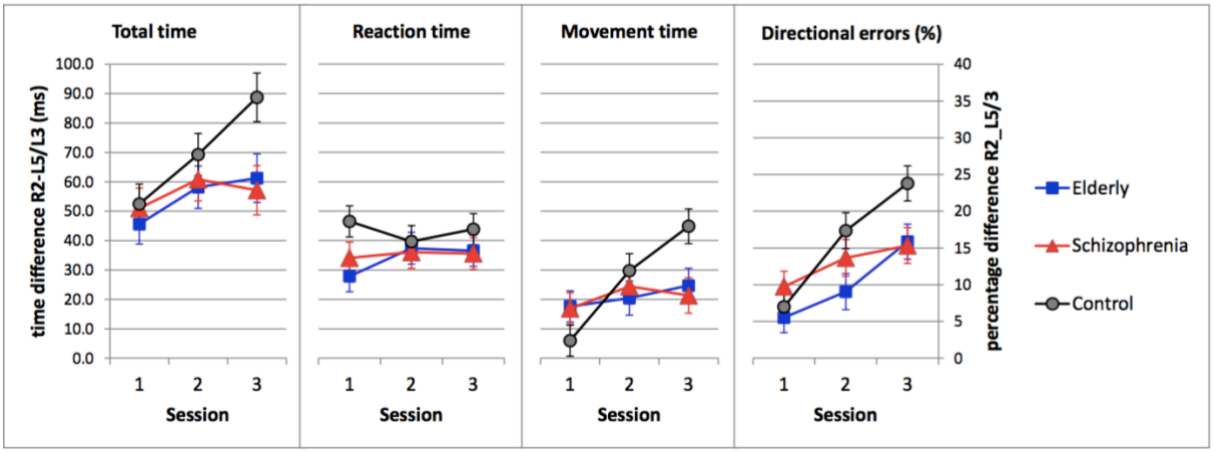

Figure 3. Amount of learning at the end of the three sessions revealed by the differences between the final random block (R2) and the preceding learning block (L5 in session 1 or L3 in sessions 2 and 3).

Sequence learning per block

The design of the present study, by including random trials in the learning blocks with fixed sequence trials, made it possible to test whether the groups differed in their learning speed already in the first learning blocks and not only at the final block in a session. However, as can be seen in Fig. 2, the TT to move to the 8 random targets was higher in block R1 than the TT to the 12 future fixed sequence targets (535 vs. 514ms, F (1,86) =53.81, p <.0001). Therefore, to test whether the measure of learning, i.e., the difference between random and fixed trials, is larger in blocks L2 till L5 compared with the first learning block, the differences at L1 were subtracted from the differences at L2, L3, L4 and L5. The resulting group means are displayed in Fig. 4. ANOVA on these data showed no group effect (F (2,86) =0.11, p =.89), the block effect was significant (F (3,84) =11.85, p <.0001), the significant block by group interaction (F (6,168) =2.16, p =.049) was only caused by a cubic contrast (p =.007), and the linear and quadratic contrasts (p =.293 and p =.793) were not significant. Figure 4 also shows that sequence learning could be observed already in block L2. An analysis on these corrected L2 differences demonstrated a substantial improvement in L2 (F (1,86) =42.06, p <.0001), which was equal for the three groups (F (2,86) =1.04, p =.359). This means that significant sequence learning appeared already after 5 repetitions of the 12-target sequence (in L1) in all three groups alike.

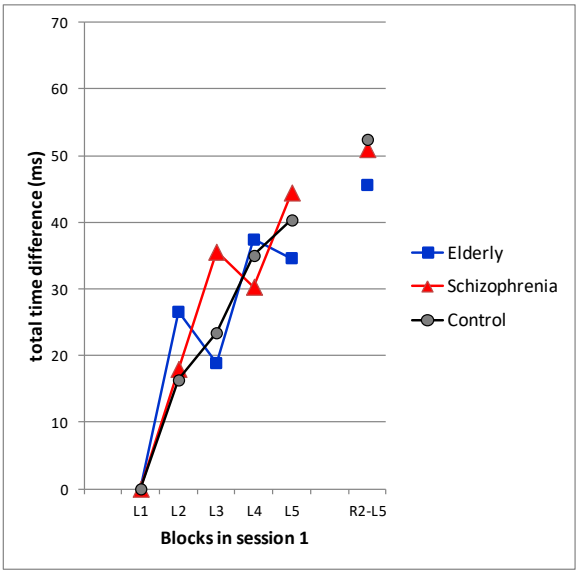

Figure 4. Difference in total time per group between random and fixed sequence trials per block (L1 to L5) in session 1 corrected for differences in L1. For comparison the R2-L5 TT differences of session 1 (presented earlier in Figure 3) are also shown.

Awareness

The three different awareness tasks are significantly different from each other, but these tasks also correlated with each other. The subjective awareness task differed significantly from the recognition task ($\chi 2$ =8.45, p =.004) and from the recall task ($\chi 2$ =4.93, p =.026), and the recognition task differed significantly from the recall task ($\chi 2$ =8.99, p =.003). The subjective awareness task correlated significantly with the recognition task (r =.30, p =.004) and with the recall task (r= .23, p= .026) and the recognition task correlated significantly with the recall task (r =.31, p =.003).

The degree to which explicit knowledge had developed over the ISL task was assessed after each session by a subjective awareness questionnaire and — only after session 3 — by a recognition test and a recall test.

In order to split the data of the three awareness tasks into the dichotomous categories 'explicit knowledge' and 'no explicit knowledge,' the participants that scored higher than a criterion were counted. This criterion was set to a positive answer to the first question for subjective awareness and to the median score over all 89 participants for the recognition and recall tests. The percentage of participants who scored higher than these criteria is presented in Table 1. Knowledge in the schizophrenia group, as compared

to the control group, was significantly lower on subjective awareness in session 1 ($\chi 2$ =4.39, p (2-sided) =.036) and session 3 (1) ($\chi 2$ =7.04, p =.008) and on the recall test ($\chi 2$ =8.96, p =.003). The elderly group was significantly higher than the schizophrenia group on subjective awareness in session 3 ($\chi 2(1)$ =5.15, p =.023) and on the recognition test ($\chi 2(1)$ =4.88, p=.027). It differed significantly from the control group only in the recall test ($\chi 2(1)$ =6.70, p=.010)

The relation between explicit knowledge and the amount of sequence learning (assessed by the TT difference between blocks R2 and L5/L3) was explored by calculating correlations (Spearman's ρ and for recall Pearson r). These correlations are presented in Table 1. Correlations higher than or equal to 0.31 are significant (without correcting for multiple testing). The first and most striking result is that subjective awareness correlated significantly with amount of sequence learning only in the elderly and control groups. For the schizophrenia group, this correlation was even close to zero at the first session. This agrees with the finding that the amount of sequence learning of the 12 patients with schizophrenia without subjective awareness was equal to that of the 17 patients with schizophrenia who expressed some amount of subjective awareness (TT difference R2–L5: 50 vs. 51ms; t (27) = −0.07, p =.949).

The second finding that emerges from these correlations is that the Recognition test scores had no significant relation with sequence learning in contrast with the Recall test scores. On this latter test, the median score amounted to eight of the twelve targets that were pointed out without any error. This seems to suggest a substantial amount of explicit knowledge, but it must be recognized that it took a considerable amount of time to express this knowledge. The mean TT in the recall test was 1793ms (2197, 1958 and 1223ms for groups E, S and C), while the mean TT in block L3 of session 3 was more than four times faster, i.e., 392ms (424, 436 and 316ms for groups E, S and C).

The recall task shows that in patients with schizophrenia and in elderly there is a different contribution of explicit knowledge. In Table 2 is demonstrated that there is a significant correlation between awareness on recall and the performance on RTs in patients with schizophrenia. In the elderly, on the contrary, there is a significant correlation between the recall

task and RTs and MTs and especially the amount of DEs. The elderly persons with awareness on recall (37%) had significantly better MTs and DEs, while the aware persons in the control group (68%) and schizophrenia group (32%) showed the same performance levels on MT and DE.

The elderly might have profited from their explicit knowledge by making less DE. Importantly, while in patients with schizophrenia and the elderly the better performance levels can be partly attributed to explicit learning, this is not the case for the controls.

Table 1. Degree of explicit sequence knowledge and its relationship with sequence learning.

	Session				
	1 Subjective Awareness	2 Subjective Awareness	3 Subjective Awareness	3 Recognition Test	3 Recall test
Percentage of participants scoring above the criterion score					
Elderly	70	83	90	67	37
Schizophrenia	59	76	66	38	32
Control	83	90	93	57	68
Correlation coefficients with sequence learning					
Elderly	0.48*	0.76**	0.52*	.28	.54*
Schizophrenia	0.03	0.25	0.17	.21	.43*
Control	0.52*	0.53*	0.31*	-.05	.34*

Percentage of participants per group scoring above the criterion score on Subjective Awareness in sessions 1, 2 and 3, and on the Recognition and Recall tests in session 3.

Correlation coefficients between the final measure for sequence learning (TT difference of R2 - L5 or L3) and awareness scores on Subjective Awareness in session 1, 2 and 3, and on the Recognition and Recall tests in session 3. Correlations higher than or equal to 0.3 are significant and marked by an asterisk (*). Correlations higher than 0.6 are marked by a double asterisk (**).

Table 2. Correlation coefficients of recall with the amount of sequence learning in session 3.

Correlation Recall – amount of sequence learning

	TT	**RT**	**MT**	**DE**
Elderly	.54*	0.35*	0.45*	0.66**
Schizophrenia	.43*	0.61**	0.03	0.03
Control	.34*	0.27	0.22	0.27

Correlation coefficients between the amount of learning by the difference in TT (total time), RT (reaction time), MT (movement time) and amount of DE (directional errors) of the last random block (R2) and the preceding learning block (L3) and the Recall task in session 3. Correlations higher than or equal to 0.3 are significant and marked by an asterisk (*). Correlations higher than 0.6 are marked by a double asterisk (**).

DISCUSSION

This study investigated ISL in patients with schizophrenia, elderly subjects and young healthy controls. The main findings of the study were that all subjects showed an equally increasing amount of learning on two consecutive test days. However, when retested after 1 week, no further learning improvements were detected in patients with schizophrenia and the elderly in contrast to the controls who showed an ongoing linear improvement in their performance on the learning task. Explicit sequence recall was correlated with sequence learning in all subjects, indicating that the impaired performance in patients with schizophrenia and elderly subjects after 1week might be related to explicit learning deficits.

In general, sensorimotor learning (on random trials) was found to be preserved in the elderly and in patients with schizophrenia. The elderly subjects were slower on the first random trials of each session, which might indicate difficulties to initiate the task or a poorer between-session sensorimotor skill consolidation in the elderly, although this group difference disappeared in the following learning blocks. The elderly showed more task-specific sensorimotor learning than patients with schizophrenia and controls during sessions 1 and 2, which is in line with previous SRTT findings in ageing[129]. This enhanced sensorimotor learning may be explained as a compensational mechanism for the explicit learning deficits in ageing[140] as compensatory increases in motor cortical and the cerebellar activation has been observed in older individuals[141].

The control group superiority on session 3 might be explained by the combination of sequence-specific learning as their amount of DEs was only reduced on fixed trials, indicating that they anticipated the next target and moved the pen in the anticipated direction, and task-specific learning, as there was a general increase in movement speed. The elderly had also a lower amount of DEs only on fixed trials which might indicate that they were able to orient their attention to the next stimulus and learn the sequence, but they seemed not to benefit actively from this knowledge by increasing movement speed. Patients with schizophrenia had less DEs on both fixed and random trials, which suggests that their slower MTs enabled them to wait more patiently until the next target appeared instead of actively searching for the next target. This result is in line with previous

findings that patients with schizophrenia demonstrate greater difficulty to disengage their attention from attended stimuli[43] and show a delayed anticipatory orienting toward subsequent stimuli[142].

Although the elderly were found clinically healthy and free from disorders that might impair task performance, factors such as arthritis, sarcopenia, atrophy of the basal ganglia and a declining dopaminergic function which might have contributed to the slowing of their hand movements[143] could not be excluded. In schizophrenia, the slower MTs could be influenced by psychomotor slowing that is inherent to the illness[7] and by extrapyramidal symptoms due to dopaminergic antagonist action of most antipsychotic drugs[10,144]. All patients were stably treated with antipsychotic medication at the time of testing; however, we found no dose–response relationship between the used antipsychotic dosage (in chlorpromazine equivalents) and sensorimotor performance on the IPLT.

The 12-target sequence was learned already after 5 repetitions on the first learning block in all groups. This finding is like the findings of Nissen and Bullemer (1987)[126] who found that sequence learning of a 10-trial sequence occurs after 6 sequence repetitions. The relatively fast learning of the sequence may be explained by the spatial character of our task as studies that used simpler but less spatial sequences reported that 25–40 sequence repetitions were needed[145].

As most of the participants noticed that the targets were not random and the number of aware persons increased across sessions, it can be argued that a variable amount of explicit sequence learning might have influenced the IPLT results.

As expected, both patients with schizophrenia and elderly subjects demonstrated less explicit learning, but the nature of this deficit probably varied among both groups. Subjective awareness seemed to improve the IPLT performance in the controls and the elderly, but not in patients with schizophrenia. The recognition task did not correlate with the IPLT performance in any group, and recall was positively correlated with the IPLT performance in all groups. The apparently (but not significantly) smaller correlation of recall with IPLT performance in controls is counterintuitive but might be explained by the generally high score of recall in the controls. The higher amount of sequence learning in the controls on

session 3 might be explained by more subjective awareness and the capacity to use this knowledge actively. The elderly showed a normal subjective awareness but had an impaired capacity to move the pen quickly in the anticipated direction, and the patients with schizophrenia demonstrated already deficits in the subjective knowledge of a fixed pattern. As the patients had a normal performance on session 1 and on this session, there were no significant performance differences between aware and unaware patients, this supports our conclusion that ISL is preserved in schizophrenia. The few patients with schizophrenia who demonstrated explicit recall on session 3 might have used this knowledge to predict the next target's location, while the elderly subjects used this knowledge mainly to improve their movement time.

In a recent study, the existence of ISL was altogether questioned as the authors found that only participants who did not learn the sequence explicitly did also not learn it implicitly and vice versa[145]. In contrast, our study demonstrates that the participants (2 controls, 3 elderly subjects and 10 patients with schizophrenia) without any awareness on session 3 nevertheless showed a significant amount of sequence learning ($p = 0.003$).

There are some limitations concerning the awareness tasks as the interpretation largely depends on the sensitivity of the utilized task. Verbal report by a subjective awareness questionnaire is the most frequently used task, but it is often influenced by the patient's cooperativeness and self-confidence about the sequence. Subjects might be aware of parts of the sequence that are not addressed by the questions, and, alternatively, answering affirmatively might be the result of a positive response bias. To maximize the detection of explicit knowledge, more objective, forced-choice tasks have been developed[146]. In our study, recall had the largest correlations with IPLT performance, but this task is not often used in other studies, not consistently conducted and prone to contamination by implicit sequence knowledge such as guessing based on a feeling of familiarity and sensorimotor practice effects[147].

Although it is difficult to rule out the effect of reduced motivation, we conclude based on our observations during the IPLT and other neurocognitive tasks that it was unlikely that a lack of motivation accounts for the drop in performance on session 3. As only patients who were able to

complete the test batteries were included, our results cannot be generalized to the whole population of schizophrenic patients.

Finally, we remark that the positive correlation between the awareness and IPLT performance does not automatically imply a causal relation: it remains uncertain whether sequence awareness facilitates the performance on the IPLT. It is possible that the IPLT score improved due to explicit knowledge as our observation of DEs in controls shows that they must have moved the pen anticipatorily. However, it is equally possible that participants who learned better implicitly had a better awareness at the end due to active searching based on an implicit feeling of familiarity. The next target might also have appeared so quickly that participants did not have adequate time to benefit from their explicit knowledge: TTs during recall were generally fourfold higher than during the IPLT because here participants were instructed to actively find the next stimulus instead of working as fast as possible. It is most likely that both factors influenced each other.

The current study puts the cognitive capacities of patients with schizophrenia and healthy ageing in an optimistic clinical perspective. Patients with schizophrenia and elderly subjects had a similar task performance in the first two sessions but seemed to utilize different working strategies. As patients with schizophrenia showed less subjective awareness and the elderly seemed to have rather problems in using this knowledge actively, it might be interesting whether rehabilitation programs focusing on increasing awareness and how to utilize it (e.g., improving the active verbalization of possible underlying task rules and structures) provide benefiting results in both groups.

CONCLUSION

On the short term, sequence learning is preserved in patients with schizophrenia and elderly controls and there seems to be no effect of awareness which endorses our hypothesis that implicit sequence learning is preserved in patients with schizophrenia and elderly subjects. Although our study methods do not allow us to conclude that the deficit which becomes apparent on session 2 and especially on session 3 is the result of crescent explicit sequence knowledge in the healthy controls, the correlations of IPLT performance with the measures of awareness make this assumption more plausible. Interestingly, both groups did utilize their smaller but existent amount of explicit awareness in order to improve their task performance, seemingly by employing different strategies.

The current study underlines that there continues to be a bias in the interpretation of implicit sequence learning studies. Further research which aims at disentangling the explicit learning component in these studies might bring to the proof whether ISL performance deficits in schizophrenia can be attributed to a deficit in explicit learning.

CHAPTER VI – SENSORIMOTOR ADAPTATION

Impaired Sensorimotor Adaption in Schizophrenia in Comparison to Age-Matched and Elderly Controls

This chapter has been published as:

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Impaired Sensorimotor Adaption in Schizophrenia in Comparison to Age-Matched and Elderly Controls

ABSTRACT

Background: The “cognitive dysmetria hypothesis” of schizophrenia proposes a disrupted communication between the cerebellum and cerebral cortex, resulting in sensorimotor and cognitive symptoms. Sensorimotor adaptation relies strongly on the function of the cerebellum.

Objectives: This study investigated whether sensorimotor adaptation is reduced in schizophrenia compared with age- matched and elderly healthy controls.

Methods: Twentynine stably treated patients with schizophrenia, 30 age-matched, and 30 elderly controls were tested in three motor adaptation tasks in which visual movement feedback was unexpectedly altered. In the “rotation adaptation task” the perturbation consisted of a rotation (30° clockwise), in the “gain adaptation task” the extent of the movement feedback was reduced (by a factor of 0.7) and in the “vertical reversal task,” up- and downward pen movements were reversed by 180°.

Results: Patients with schizophrenia adapted to the perturbations, but their movement times and errors were substantially larger than controls. Unexpectedly, the magnitude of adaptation was significantly smaller in schizophrenia than elderly participants. The impairment already occurred during the first adaptation trials, pointing to a decline in explicit strategy use. Additionally, post-adaptation aftereffects provided strong evidence for impaired implicit adaptation learning. Both negative and positive schizophrenia symptom severities were correlated with indices of the amount of adaptation and its aftereffects.

Conclusions: Both explicit and implicit components of sensorimotor adaptation learning were reduced in patients with schizophrenia, adding to the evidence for a role of the cerebellum in the pathophysiology of schizophrenia. Elderly individuals outperformed schizophrenia patients in the adaptation learning tasks.

INTRODUCTION

Sensorimotor abnormalities are inherent symptoms of schizophrenia and include coordination problems, neurological soft signs, psychomotor retardation, dyskinesias, catatonia, and Parkinsonism[5–7]. These abnormalities often precede a first psychotic episode and can therefore serve as prodromal warning signs. In addition, they are predictive of illness prognosis, associated with worse antipsychotic side effects, cognitive disturbances, and negative symptoms[5,19,148]. As motor symptoms often do not ameliorate with antipsychotic treatment, they are now increasingly studied as biomarkers to aid the development of more appropriate treatment options[7,23,149]. The importance of studying sensorimotor symptoms is highlighted by the recent addition of a sensorimotor domain as part of the Research Domain Criteria framework of the National Institute of Mental Health[150,151] which aimed to further explore the complex neurobiological mechanisms in disorders such as schizophrenia[5,12,14,152,153].

In the current study, we focused on sensorimotor adaptation, which refers to the subject's ability to adjust well-trained movements to (un)expected environmental changes[154], such as playing tennis with strong side wind, getting used to new spectacles or walking on cobblestones on high heels. The study of sensorimotor adaptation in schizophrenia is clinically interesting because these deficits have been linked to a reduced "sense of agency," that is, the ability to distinguish between self-caused sensations and those due to external sources. This form of failure in self- or error monitoring could in part explain some psychotic symptoms such as paranoid hallucinations[155], incoherent language, and formal thought disorders in schizophrenia[156].

On a neurobiological level, the cerebellum has been implicated in this form of error-based sensorimotor learning as part of an integrated network including the prefrontal cortex, premotor and primary motor cortices, parietal cortex, thalamus, and basal ganglia[157–159]. Evidence for the role of the cerebellum in sensorimotor adaptation has been provided by functional MRI investigations and neuropsychological studies where impaired adaptation is demonstrated in individuals with cerebellar degeneration[150,151,160,161].

In schizophrenia research, Andreasen proposed a cognitive dysmetria model in which a disruption to the cortico-cerebellar-thalamic-cortical circuit underlies a broad set of sensorimotor and cognitive dysfunction. In this circuit, the cerebellum plays a primary coordinative role[27,162–166]. A meta-analysis of magnetic resonance spectroscopy studies in schizophrenia has shown increased glutamate levels in the cerebellum[167]. It has been argued that cerebellar abnormalities in schizophrenia might be restricted to sensorimotor symptoms rather than cognitive processes[168] but a recent meta-analysis of functional neuroimaging studies demonstrated dysfunctional cerebellar activation in schizophrenia both during cognitive (e.g., working memory, language, emotion processing, and executive function) and motor skill learning tasks[12,25]. Taken together, there is evidence for cerebellum- related motor dysfunction in schizophrenia.

Surprisingly, sensorimotor adaptation has received relatively little attention in schizophrenia research and the results are mixed. Reduced saccadic adaptation was demonstrated by Picard et al.[169] and Coesmans et al.[170]. Knoblich et al.[156] found impairments in the detection of a perturbation, but not in the ability to automatically compensate for it in a gain task. Rowland et al.[171] and Bansal et al.[155] demonstrated intact adaptation in reaching tasks and mirror drawing has been found to be impaired, dependent of the type of antipsychotic drug used for treatment[172]. In other words, sensorimotor adaptation in schizophrenia needs further exploration.

Recent research supports the theory that schizophrenia might be a neurodegenerative disorder with genetic, functional-organic, and neuroanatomical features of accelerated ageing[51,52,173], sharing similarities with elderly individuals. A decline in sensorimotor adaptation in the elderly has been well documented[57,59]. Elderly individuals show mainly intact implicit learning but impaired explicit learning in visuomotor adaptation tasks[57].

The present study investigated adaptation of fast ballistic arm movements during two variants of a reaching task. Following initial training, visual feedback of the movement was unexpectedly altered (rotated or distorted). Theoretically, immediately after the introduction of a perturbation, subjects will generate an explicit (cognitive) strategy in order to compensate for an

observed error. Subsequently, a more implicit learning process should lead to further automatic recalibration of the movement[40,58]. When the perturbation is removed, there is a post-adaptation phase where a negative aftereffect (compensatory opposite movement) can provide a measure of the amount of previous implicit adaptation learning. Earlier studies did not incorporate such a post-adaptation phase.

Sensorimotor adaptation is a combination of explicit processes, characterized by intentional movement control, and implicit mechanisms, characterized by corrections based on sensory prediction errors. In order to differentiate better between implicit and explicit processes during sensorimotor adaptation, a mirror drawing task, the "vertical reversal task" was also included. This is a more "explicit," cognitive variant of a reaching adaptation task[174]. This task involves the acquisition of a new strategy (reversing the writing direction by 180°) instead of recalibration of a movement[175]. In addition, subjects were provided explicit information about the nature of the distortion.

Patients with schizophrenia were compared with healthy controls and healthy elderly individuals. Given the "cognitive dysmetria hypothesis" and the perception of schizophrenia as an "agency disorder," we hypothesized that patients with schizophrenia would demonstrate deficits on sensorimotor adaptation tasks. As deficits in explicit learning are well-known in schizophrenia, we hypothesized that patients would demonstrate more deficits on the explicit processes during sensorimotor adaptation. Comparison with the elderly was made in order to explore whether illness-related impairment of sensorimotor adaptation in schizophrenia is matched by comparable age-related deficits.

METHODS

Participants

Twentynine patients with schizophrenia, 30 healthy age- matched and 30 elderly controls participated in the study (Table 1). All candidates provided written informed consent. All patients were stably treated with antipsychotic medication for at least 6 weeks, with no more than two different antipsychotic drugs used at the same time. At the time of testing, patients were judged to be in stable clinical condition through subject interview and medical history review by a trained clinician. Symptom severity of patients was rated at screening by a trained psychology assistant using the Scale for the Assessment of Negative Symptoms and Positive Symptoms (SANS- SAPS). This study was reviewed and approved by the institute's Ethics Committee and is registered at ClinicalTrials.gov: NCT01788436.

Task Design

Participants used a non-inking pen on a digitizing writing tablet (WACOM 1218RE) which controlled a cursor (a green dot with 4 mm diameter) on a computer screen above the tablet. They were required to make single movements from a start position toward a target location.

Rotation and Gain Adaptation Task - The rotation and gain adaptation task were based on the ones used by Schaefer et al. [44]. Participants were required to make a fast pen/hand movement beginning at a yellow starting circle toward a blue-filled circle over a distance of 10cm, and then return the pen to the starting circle. The blue-filled circle was one of three possible targets. Participants were instructed not to react as quickly as possible but rather to move as fast as possible with one simple straight "shooting" movement. The target circles were 25 mm in diameter positioned either directly above the starting circle, 45° to the left or 45° to the right of the starting circle. The three possible targets were presented in random order. Each task began with three 12-trial "baseline" practice blocks (blocks B1–B3) consisting of straightforward movement to the target. Following that (without notice and interruption), four 12-trial "adaptation" blocks (blocks A1–A4) were administered, where visual feedback was altered. These adaptation trials were immediately followed (again without informing the

participants) by two 12-trial "post-adaptation" blocks (blocks P1–P2) where the perturbation was completely removed.

In the rotation adaptation task, adaptation trials consisted of a 30° clockwise rotation around the start position of the cursor relative to the direction of their hand movement. This caused directional errors with the subject finishing next to the target in the direction of the rotation. In the gain adaptation task, movement feedback was reduced by a factor of 0.7, which caused undershooting and required participants to make a much larger movement to reach the target.

In all normal conditions, a pen movement on the tablet of 100 mm was displayed as a cursor movement on the screen of about the same size (i.e., 100 mm). During adaptation trials, a 100-mm pen displacement resulted in a 70-mm cursor displacement on the screen. Participants therefore had to make a larger (1/0.7) movement to the target: not of 100 mm but of 143 mm.

During the adaptation trials, returning to the starting point was unperturbed. The cursor was masked until it reached the area of the starting circle; whereby the screen turned green except for a small rectangle around the starting point. Had there been visual feedback at this stage, the unperturbed cursor position would have a sudden visible jump at the start of the movement in order to get back to the start position.

Vertical Reversal Task - In the vertical reversal (mirror) task, like the adaptation tasks, the cursor had to be moved as fast as possible toward a 10 mm-diameter circle. Four possible targets were displayed at the corners of a 20-mm-sided square position in the middle of the screen. A trial started as soon as one of the open circles turned red indicating a target. The trial ended when the cursor was held inside that target circle for 100ms. This was signaled by a beep and a change of the target color to yellow. After an interval of 100–108ms the next trial started with one of the other three possible targets turning red.

Three 12-trial "baseline" practice blocks (blocks B1–B3) were presented without perturbation. Following that, eight 12-trial "adaptation" blocks (blocks A1–A8) were completed. In these trials, participants were informed about an upcoming perturbation, which consisted of a reversal of the visual

feedback along the vertical axis, creating a “flipped” image as if drawing in a mirror: left- or rightward pen movements remained normal whereas up- or downward pen movements were reversed by 180°. For the five last 12-trial “post-adaptation” blocks (blocks P1–P5), participants were informed that the visual feedback would be normal again.

The tasks were administered following a battery of similar psychomotor tasks which were all performed on a digitized writing tablet. Results of the other tasks are reported previously [5–28]. This battery was conducted over three sessions. Session 1 and 2 took place over 2 consecutive days and session 3 took place 1 week later. The rotation adaptation task was administered once in session 2 and the gain adaptation task was administered once in session 3, each task taking 5–7 min to complete. The vertical reversal task was administered on all three sessions. It took about 5–8 min in session 1 and 4–5 min during later sessions.

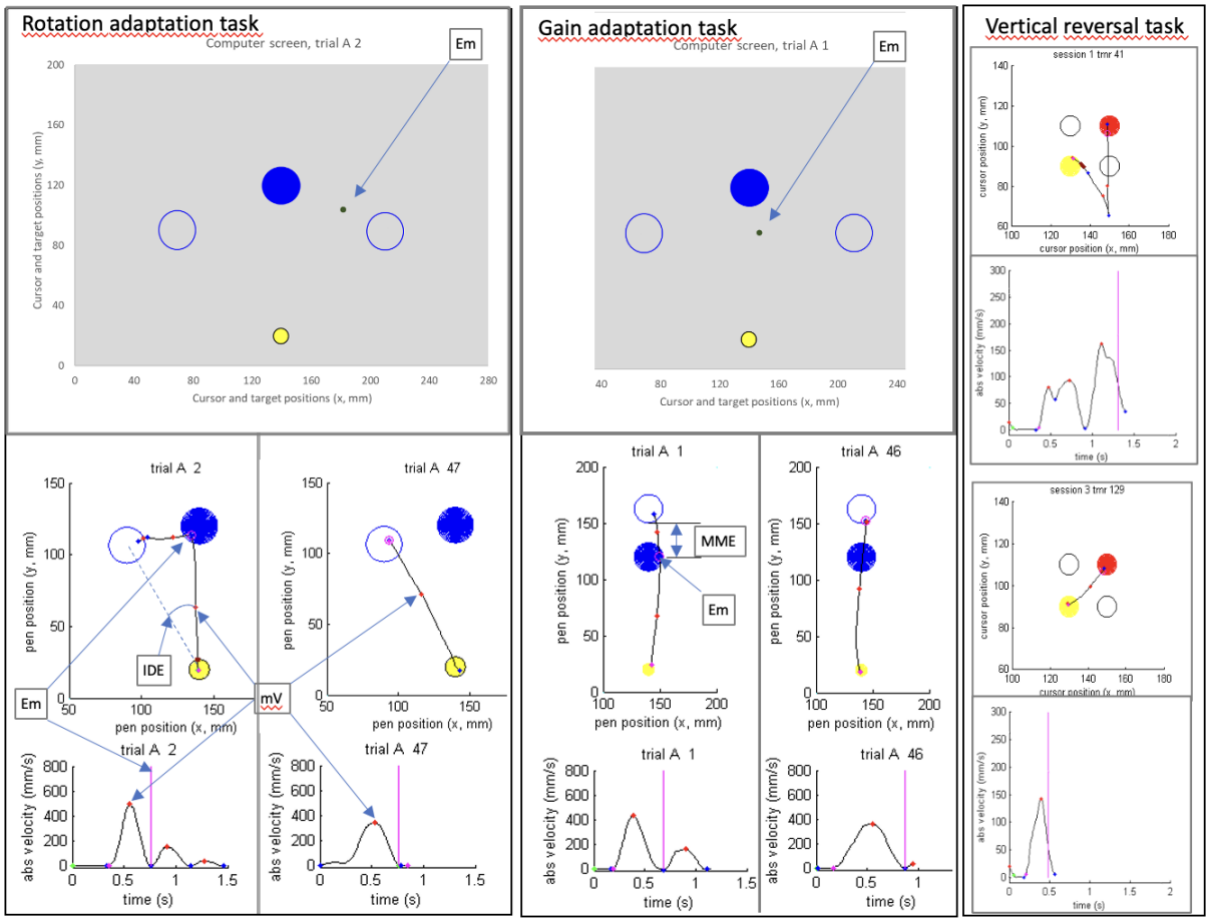

Figure 1: Illustration of the three tasks, including an example of a pen position and trajectory. In addition, graphs are presented depicting absolute velocity over time.

In the rotation adaptation task, participants moved the small green cursor with a fast ballistic movement (the “main” movement) beginning at the starting yellow circle and ending at the filled blue target circle. Movements of a control participant are illustrated. The cursor is depicted at the position of the end of the main movement (“Em”) in the second adaptation trial (A2). The cursor was rotated 30° clockwise and additional compensatory pen movements were needed to reach the target in trial A2. At the end of the adaptation period (trial A47) this participant had learned to start the movement in the right direction, aiming at the virtual target (open circle). The initial direction error (IDE) was measured at the point where maximal velocity was achieved.

In the gain adaptation task, the movement of the cursor on the screen was reduced by a factor of 0.7. Therefore, the main movement of trial A1 ended (Em) well in front of the goal which made an extra corrective movement necessary. The main movement error (MME) was measured between the pen position at Em and the edge of the virtual target.

An example of the first and last adaptation trial in the vertical reversal task is illustrated. Cursor trajectory and pen velocity are shown (pen trajectories were vertically reversed cursor paths).

Participants only saw the cursor not its path. On the first adaptation trial, the control participant made a diagonally upward pen movement. As a result of the vertical reversal, this resulted in an initial oblique downward cursor trajectory that was quickly corrected subsequently. In the final trial, the participant had learned to make the correct oblique downward movement in order to move the cursor along a straight line diagonally upward to the target. For more detailed examples of the task design, see online supplementary Fig. 1–9 (for all online supplementary material, see www.karger.com/doi/10.1159/000518867).

Kinematic Data

Pen movements were recorded at 200 Hz and 0.2 mm spatial accuracy. Analysis software was written in MATLAB 7.8.0. Movement time (MT), IDE, and movement errors (MME) were the main dependent variables.

MT was defined as the time between crossing the border of the starting circle and crossing the border of the target circle. Movements in each trial

had to end in the target circle in order to start the next trial. Therefore, inefficient trajectories resulted in prolonged movement duration. Trials lasting >3 s were accounted as a true error. These true errors occurred in 1–4% of the trials. Groups did not differ significantly on error percentages.

The IDE in the rotation adaptation task was defined as the angular deviation from a straight line between start and target. It was measured at the pen position on peak velocity. The MME in the gain adaptation task was the distance between the pen position at the end of the initial ballistic movement (the main movement) and the target position. The first minimum in absolute pen velocity after the peak velocity was used as the end of this ballistic movement.

Statistical Analysis

All data were analyzed in SPSS version 25 with repeated measures ANOVA's (GLM) on trial blocks as the within-subject factor and groups as the between-subject factor. Group differences with the control group were tested with planned simple contrasts. Bonferroni post hoc analysis was used to compare the schizophrenia with the elderly group. Alpha was set at 0.05.

RESULTS

Demographics and baseline results

General characteristics of the three study groups, mean SANS, and SAPS scores of the patient group, mean MTs at the baseline blocks of each adaptation task and corresponding group differences (simple contrasts, ANOVA) per task are shown in Table 1. At baseline, the schizophrenia and elderly group performed similarly and were significantly slower than the control group. These baseline differences were corrected by subtracting the third baseline block mean from all adaptation and post-adaptation values per session for each individual subject (MT difference, MTd).

Table 1. Group characteristics, average SANS and SAPS scores and baseline MTs in the three adaptation tasks.

	Schizophrenia (S)	**Elderly (E)**	**Control (C)**			
N	29	30	30			
Sex (female – male)	10-19	10-20	10-20			
Age (Mean (SD) yrs)	36.8 (7.7)	69.3 (3.9)	36.8 (8.6)			
Average SANS score (SD)	26.2 (18.0)					
Average SAPS score (SD)	12.0 (18.5)					
MT Baseline (ms)				**F (2,86)**	**p**	**contrast**
Rotation adaptation	405	402	320	4.47	.014	(S=E)>C
Gain adaptation	383	369	283	7.02	.002	(S=E)>C
Vertical reversal	243	242	180	10.69	<.0001	(S=E)>C

Rotation Adaptation Task

Movement Time

Following the introduction of the 30° clockwise rotation, movement times (MTd) suddenly became much longer in each group, and from then on decreased gradually as a result of adaptation learning. The schizophrenia

group had the longest MTd on each adaptation block (A1–A4) (MTd: S>C: p =0.004; S>E: p =0.033; E=C: p =0.708) but the adaptation rate (MTd decrease over adaptation blocks; block*group), was equally strong in all three groups (see Fig. 2; Table 2). As can be seen in Figure 2 and Table 2, there was a significant aftereffect in each group demonstrated by prolonged MTd in the first post-adaptation block compared with the last adaptation block (A4–P1). These aftereffects were not significantly different between groups. The decrease in MTd from P1 to P2 was also significant and similar for all three groups.

Initial Direction Error

Mean IDEs on the first trials of A1 were close to 30° (group S: 26°, group E: 27° and group C: 26°). In subsequent adaptation trials, patients with schizophrenia made larger errors than controls (p =0.024) whereas the elderly did not differ significantly from the controls (p =0.240). The IDE decrease over adaptation blocks was significant and similar for the three groups (see Fig. 2, right panel). In the post-adaptation condition, a strong aftereffect (IDEs in the opposite direction) was found in all three groups (see Table 2), and interestingly none of the groups returned entirely to the straight (0° angle) direction of baseline block B3.

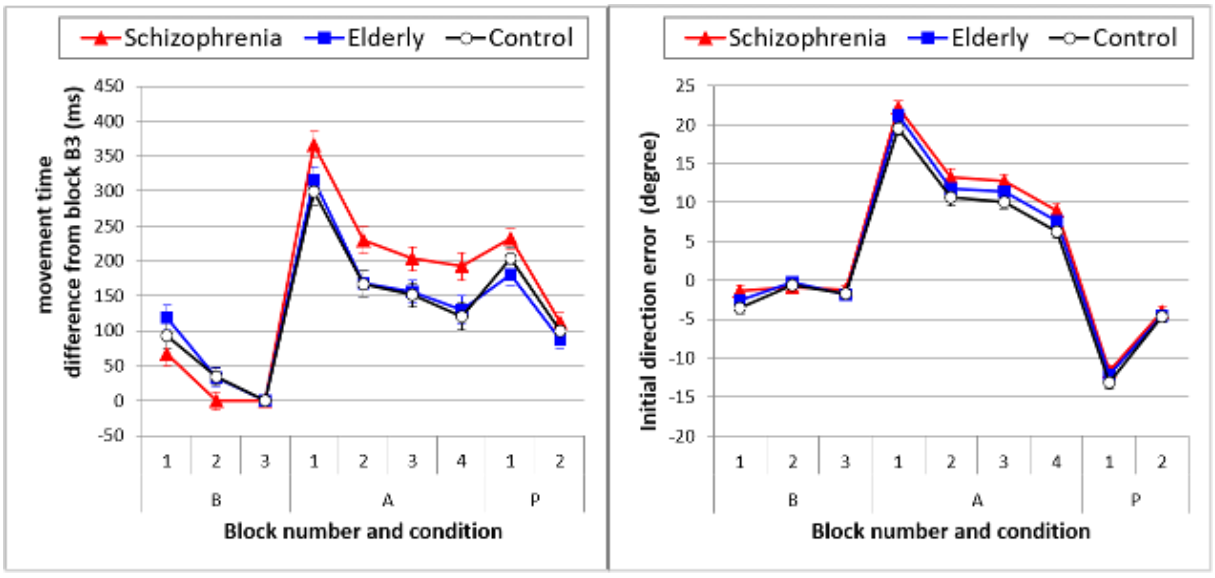

Fig. 2: Rotation adaptation task. Group means and standard errors (SE) of MTd (left panel) and IDE (right panel) on baseline (B1-B3), adaptation (A1-A4) and post-adaptation (P1-P2) trial blocks.

Table 2. Rotation adaptation task. Results of analyses of variance (ANOVA) of MTd and IDE on adaptation blocks (A1-A4), between A1 and P1 and on post-adaptation blocks (P1-P2)

		A1-A4			**A4-P1**			**P1-P2**		
		F	**df2**	**P**	**F**	**df2**	**P**	**F**	**Df 2**	**p**
MTd	Block	68.50	83	< 0.0001	24.60	85	< 0.0001	219.18	85	< 0.0001
	Block*group	0.33	166	0.918	1.28	85	0.283	1.21	85	0.303
	Group	5.16	85	0.008	4.74	85	0.011	2.31	85	0.106
IDE	Block	346.06	83	< 0.0001	1742.7	85	< 0.0001	226.36	85	< 0.0001
	Block*group	0.10	166	0.996	0.63	85	0.535	0.33	85	0.719
	Group	2.66	85	0.076	1.71	85	0.186	0.55	85	0.578

Gain Adaptation Task

Movement Time - Like the rotation adaptation task, patients with schizophrenia demonstrated the longest movement times during adaptation (MTd: S>C: p =0.001; S>E: p =0.006; E=C: p =0.615), but the decrease over adaptation blocks was significant and equally strong in all three groups (see Fig. 3; Table 3). Controls and elderly subjects showed a positive aftereffect (MTd increase from A4 to P1 in Fig. 3) in contrast to the schizophrenia patients. This block*group interaction was significant (see Table 3). In addition, controls and elderly participants showed a significantly larger improvement in MTd on post-adaptation trials (p =0.001).

Main Movement Error - The gain diminution required an active movement extension from 100 to 143 mm on the adaptation trials. On the first adaptation trial of A1, there was an average undershoot of 41 mm which was equal in all groups. On subsequent trials, however, the undershoot reduced quickly to about 10–15 mm in the controls and elderly group, in contrast to the schizophrenia patients who kept making larger undershoots (S>C: p =0.004; E=C: p =0.205; S>E: p =0.0001) (see Fig. 3, right panel). The decrease of MME over adaptation blocks was significant and similar in the three groups. On the first post-adaptation trial of P1, all groups showed an aftereffect (overshoot in group S: −17 mm, group E: −22 mm, group C: −27 mm), which diminished quickly after about 4 trials in all groups. The post-

adaptive improvement was significant and similar for all groups (see Table 3).

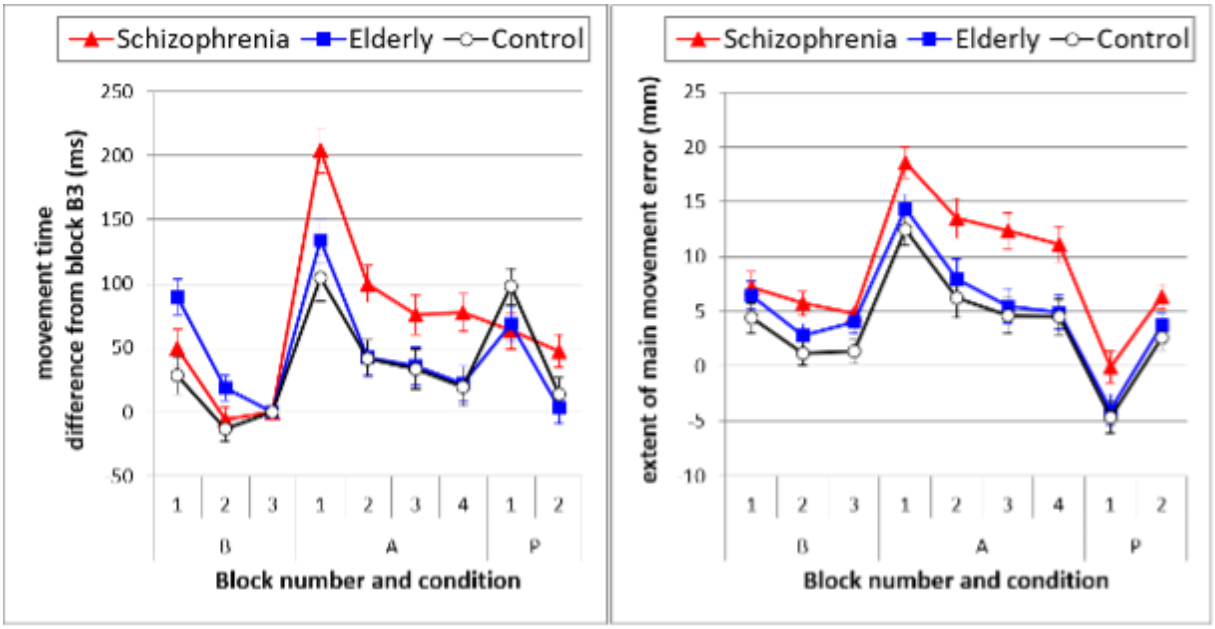

Fig. 3: Gain adaptation task. Group means and SE of MTd (left panel) and the extent of main movement error (MME, right panel), during baseline (B1-B3), adaptation (A1-A4) and post-adaptation (P1-P2) trial blocks. Undershoots (mostly during adaptation) are reflected as positive error values and overshoots (mostly during post-adaptation) as negative error values.

Table 3. Gain adaptation task. Results of analyses of variance of MTd and ME on adaptation blocks (A1-A4), between A4 and P1 and on post-adaptation blocks (P1-P2)

		A1-A4			**A4-P1**			**P1-P2**		
		F	df2	p	F	df2	P	F	df2	p
MTd	Block	59.46	81	< 0.0001	15.21	83	0.0002	54.01	83	< 0.0001
	Block*group	1.16	162	0.333	8.08	83	0.001	7.17	83	0.001
	Group	7.75	83	0.001	1.17	83	0.316	0.95	83	0.390
MME	Block	81.85	81	< 0.0001	244.88	83	< 0.0001	187.83	83	< 0.0001
	Block*group	0.74	162	0.619	1.33	83	0.271	0.55	83	0.581
	Group	6.11	83	0.003	4.70	83	.012	3.26	83	0.043

Vertical Reversal Task

Adaptation - Figure 4 and Table 4 show that, averaged over sessions, the control group had significantly faster MTds than schizophrenia ($p < 0.0001$) and elderly individuals ($p = 0.002$), and the latter two groups performed almost equally ($p = 0.232$). The learning effect (MTd decrease on adaptation blocks) was equal among all groups. This was so for each session, though

the group differences and learning affect slopes declined from session 1 to 3. Group differences changed over sessions. In the first session, on A1, controls were significantly faster in comparison to the schizophrenia (p =0.022) and elderly (p =0.036) group, while the latter two groups performed almost equally (p =1.00). On A2, the elderly improved more than the patients with schizophrenia (t (57) =2.07, p =0.043 [2-tailed]). In session 2, this difference between schizophrenia and elderly in MTd on A2 was smaller (t (57) =1.70, p =0.095 [2-tailed]) and it disappeared altogether in session 3 (t (57) =−0.49, p =0.628 [2-tailed]).

Post Adaptation - All groups demonstrated a fast return to baseline values during post-adaptation trials. Only on P1, some significant aftereffects could be detected, especially in later sessions (see Fig. 5). On P1 in session 1, groups performed similarly (p =0.393); however, in sessions 2 and 3, there were significant group differences (resp. p =0.001 and p =0.014). The controls showed a larger aftereffect (a relatively large MTd on P1) in session 2 and especially in session 3, whereas the elderly displayed an aftereffect only in session 3 (t (29) =2.45, p =0.021 [2-tailed]). Patients with schizophrenia did not demonstrate any aftereffect in any session.

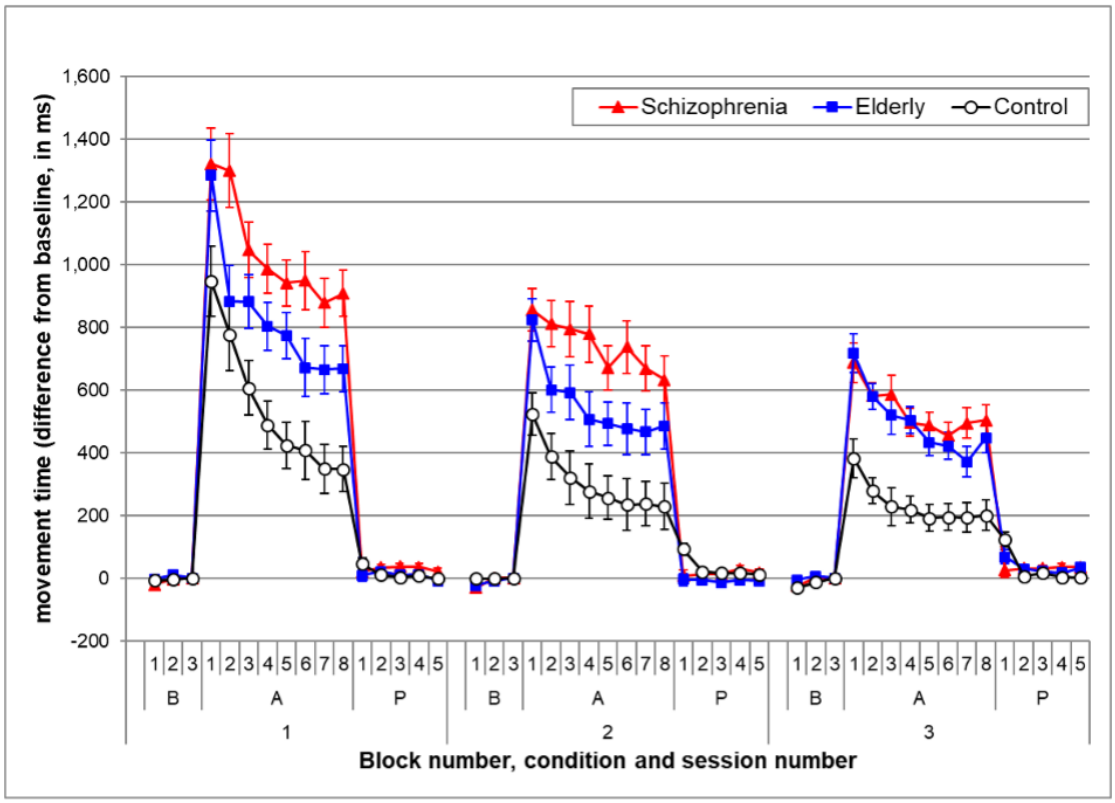

Fig. 4: Vertical reversal task. Group means (and SE) of MTd on baseline (B1-B3), adaptation (A1-A8) and post-adaptation (P1-P5) trial blocks in the three sessions.

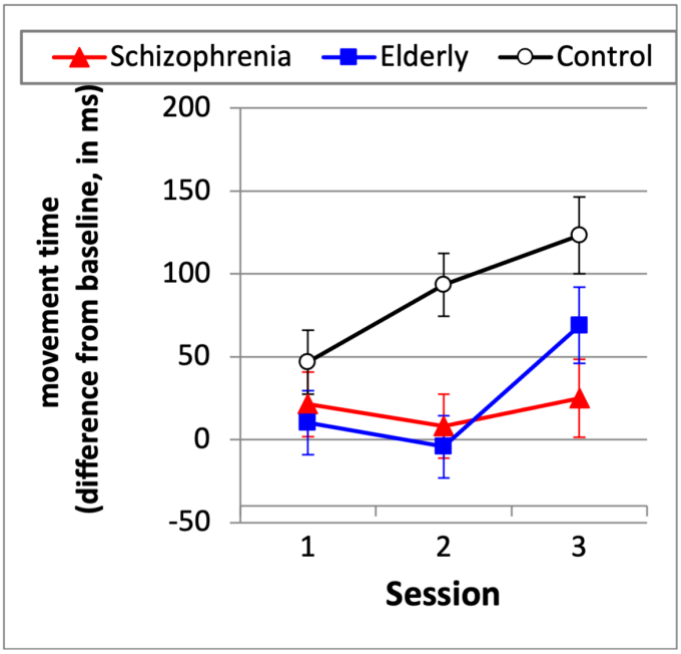

Fig. 5: Vertical reversal task: aftereffects. Group means (and SE) of MTd on P1 in each session.

Table 4. Vertical reversal task. Results of analysis of variance (ANOVA) on MTd on adaptation trials (A1-A8), post-adaptation trials (P1-P5) and on block P1.

Block	**A1-A8**			**P1-P5**			**P1**		
	F	**df2**	**p**	**F**	**df2**	**p**	**F**	**df2**	**p**
Session	85.93	85	< 0.0001	5.67	85	0.005	5.38	85	0.006
Session * group	3.73	170	0.006	2.89	170	0.024	2.08	170	0.085
Block	25.64	80	< 0.0001	3.22	83	0.017			
Block*group	0.71	160	0.765	3.01	166	0.003			
Session*block	5.10	73	< 0.0001	2.40	79	0.023			
Session*block*group	0.92	146	0.589	0.94	158	0.526			
Group	13.08	86	< 0.0001	1.50	86	0.230	6.33	86	0.003

Correlations with Schizophrenia Symptoms

Symptom severity, which was assessed by the Scale for the Assessment of Negative Symptoms and Positive Symptoms (SANS-SAPS), correlated with (1) measures of sensorimotor speed, mean baseline MT of the three tasks; (2) the effect of the perturbation during adaptation trials, mean adaptation MTd; and (3) the MTd aftereffects observed in the three tasks. The results are presented in Table 5. Four out of 9 correlations with SANS and 6 out of 9 correlations with SAPS were significant.

Table 5. Correlations of symptom severity with baseline measures of sensorimotor speed and with indices of the amount of adaptation and its aftereffects

	Correlations Spearman's rho	
	SANS	SAPS
SANS	1.000	**0.331***
SAPS	**0.331***	1.000
Baseline MT		
Rotation adaptation	**0.539****	**0.496****
Gain adaptation	**0.620****	**0.405***
Vertical reversal	0.231	0.252
Adaptation MTd		
Rotation adaptation	-0.061	0.205
Gain adaptation	**0.505****	**0.369***
Vertical reversal	0.300	**0.460****
Aftereffect MTd		
Rotation adaptation	-0.207	**-0.348***
Gain adaptation	-0.262	**-0.366***
Vertical reversal (session 3)	**0.381***	-0.272

*. Correlation is significant at the .05 level (1-tailed). **. Correlation is significant at the .01 level (1-tailed).

DISCUSSION

The aim of the study was to extend the limited evidence of impaired sensorimotor adaptation in schizophrenia. Our results demonstrated that patients displayed reduced sensorimotor adaptation compared with healthy controls.

Although they adapted to sudden perturbations in all three tasks, shown by decreased MT and errors and a similar slope over consecutive adaptation trials, movement times, and errors were substantially larger in patients than controls, even after correcting for the already slower movement speed of patients with schizophrenia and elderly at baseline. Patients needed more time to reach the target from the beginning toward the end of the adaptation period because they made larger and/or more corrective movements to compensate for errors made on the fast main movement.

While none of the groups adapted completely (movement times and errors during adaptation did not reach baseline values), controls approached more optimal values than patients. We might speculate that patients might have reached the same level as controls had more adaptation trials been presented. Adaptation was also more reduced in patients than in elderly participants.

Symptom severity, measured by the SANS and SAPS scores, correlated significantly with patient's baseline motor speed, adaptation to the perturbation and aftereffects. The significant correlations of SAPS scores with the MTd aftereffects in the rotation and gain adaptation tasks demonstrate that patients with more positive symptoms have a reduced amount of implicit adaptation learning.

The current study employed paradigmatic adaptation tasks that required the recalibration of a well-trained rapid movement in conditions where normal movement execution was perturbed. Motor commands for fast target-directed movements are thought to be controlled by an internal (feedforward) model that predicts sensory consequences of a movement. A perturbation leads to a mismatch between actual (visual) feedback and predicted (anticipatory) sensory consequences of a movement. These mismatches or "sensory prediction errors" require an update of the internal model, allowing for adaptation. For many years, this form of error-based

learning was viewed as an implicit automatic process. However, in the last 10 years, it has become clear that this form of simple learning is based on the operation of multiple learning processes[157]. Even during the very first adaptation trials, the learner may become aware of the type of perturbation that is producing his performance errors and may generate a compensatory strategy[40,176]. Therefore, visuomotor adaptation is now generally viewed as the combined action of explicit learning driven by the detection of a performance error and implicit learning of a forward model driven by prediction error[58].

Explicit learning may be deficient in the case of (1) a misdetection of the visuomotor mismatch, (2) less successful strategy planning to cope up with the perturbation, or (3) less executive control (or effort) to continuously apply a counter intuitive strategy. On the other hand, implicit learning might be reduced because the forward model that generates the sensory predictions of the internal model, (4) is less accurate, (5) is updated insufficiently throughout the trajectory (a deterioration of internal model recalibration), or (6) the detection of the mismatch between sensory prediction and movement feedback may be less precise (an inferior detection capacity of a sensory prediction error). This theoretical account of adaptation creates several (not mutually exclusive) explanations for impaired adaptation of patients with schizophrenia found in the present study.

Evidence for inefficient explicit adaptation learning in schizophrenia is provided by larger movement times and errors than controls in the first adaptation trials. In the rotation and gain adaptation tasks, immediate and fast movements (without a trace) toward a target were required, so participants had to build a new internal movement model before the start of the next trial, pointing at detection difficulties of the mismatch between self-generated movements and their consequences (explanation 1).

Other studies, where subjects had to react to altered visual feedback while drawing, examined strategy planning, and executive control (adaptation-based on online motor corrections). Fourneret et al.[177] found less efficient adaptation and Knoblich et al.[156] found no impairment in patients on adaptation tasks.

In the current more explicit vertical reversal task, patients needed more time than controls and elderly participants to reach the target. In this task, the necessary adaptation was larger (i.e., not 30°, but 180°) and participants were explicitly informed about the vertical reversion. Therefore, it would require learning of a new (mirror-reversal) movement rather than recalibration of a well-practiced movement[154,175]. On individual trials, participants employed various explicit strategies to reach the target, which were often unsuccessful. Many participants did not learn to make straight reversal movements on the diagonals. Some found the solution to split it in a horizontal part (mostly produced first) and a (reversed) vertical movement. Others persisted in initiating misdirected movements. This was particularly true for the patients, pointing at an impaired explicit strategy use in schizophrenia.

Further research on explicit adaptation learning in schizophrenia is needed. This would require a detailed measurement of explicit strategies. Taylor et al.[40] and Christou et al.[178] have developed procedures for this measurement.

Implicit learning in adaptation paradigms is derived from the measurement of aftereffects in a post-adaptation phase. The size of these aftereffects in the present study varied among the three tasks. In the rotation adaptation task, all groups demonstrated similar aftereffects of MT lengthening and error reversal. In the gain adaptation task, patients did not show this characteristic post-adaptation MT lengthening (in contrast to elderly individuals and controls) and their post-adaptation reversal from undershoot to overshoot was significantly smaller. In the vertical reversal task, patients demonstrated significantly smaller aftereffects than the other groups, especially in the last session (see Fig. 4, 5). In other words, results from the gain adaptation and vertical reversal task provide evidence for reduced implicit sensorimotor adaptation in schizophrenia.

The difference in aftereffects during the rotation and gain adaptation task may be related to specific methodological differences between these tasks. The traditional view is that adaptation is thought to occur by updating an internal model based on sensory prediction errors. However, adaptive behavior might also result from a different mechanism of "online motor corrections"[154,157,179]. In the current study, unperturbed reach movements took 283–405ms (Table 1) and previous research has demonstrated that

rapid corrective responses based on visual feedback can be made after approximately 160ms[180]. There was therefore ample time for online motor corrections during this task. During adaptation to rotation, a two-dimensional direction error could be detected and corrected much earlier (before reaching peak velocity) than a unidimensional distance error in the gain adaptation task, where an error only became apparent near the end of the ballistic movement. Therefore, the rotation adaptation task allowed for small online modifications of the movement direction during the trajectory, while such online adjustments could not be made in the gain adaptation task. As a result, adaptation learning in the gain adaptation task is thought to be driven by sensory prediction errors. This makes the gain adaptation task a more valid test for the detection of implicit adaptation learning deficits rather than the rotation adaptation task.

An alternative interpretation of the group difference on aftereffects in the gain adaptation might be the overall slower movements in patients, facilitating online corrections. Additional analyses of (baseline corrected) maximal velocity (Vmaxd) on adaptation trials did not show group differences during rotation adaptation. However, during gain adaptation, patients were slightly (and significantly; p =0.035) slower than controls. Although most of the movement time (MTd) during adaptation was caused by time-consuming extra-corrective movements, it might be possible that (some of) the patients also moved (deliberately) with lower speed, facilitating corrective movements at the end of the ballistic movement.

Furthermore, if (a subgroup of) patients did not follow the specific instruction which were to reach for the target with one fast ballistic move, but rather completed the reach task in two (or more) sub-movements, these patients would not have to change the (internal model of the) ballistic movement from baseline to adaptation and to post-adaptation, making implicit learning less necessary.

Evidence for this explanation derives from the MME, which was greater at baseline in the schizophrenia group (Fig. 3). The mean MME over baseline blocks B2 and B3 was 5.3 mm in patients and only 1.3 mm in the controls (p =0.008 [1-sided]) and correlated significantly with the SAPS score (Spearman's rho =0.42, p =0.029) but not with the SANS score (rho =0.08, p =0.704). As patients with higher positive symptoms have larger movement

errors at baseline, we might speculate that these patients build a less accurate internal model, which may explain the slower movement times in general and not only in conditions that require adaptation. An (un)conscious strategy to make reaching movements in more than one, slower sub-movement not only explains the larger movement times at baseline and during adaptation, but also why there was less implicit learning seen on aftereffects in (a subgroup of) patients.

The idea that patients with schizophrenia are less able to build an accurate internal model of specific movements was formulated as our first implicit learning explanation (nr 4). More research is needed to distinguish this interpretation from alternative explanations that focus on a deterioration of the updating of an internal model (5), a diminished utilization of internal monitoring signals of self-movement[155] or an inferior detection of a sensory prediction error as proposed by Shergill et al.[181] and Friston et al.[182–184].

The currently presented data are part of a larger study in which the same participants were tested on a large range of sensorimotor learning tasks. In a motor sequence learning task, patients with schizophrenia demonstrated a minor reduction in learning, which became apparent only after extensive training and could be attributed to a deficit in explicit learning[64]. In two other tasks investigating implicit learning, a sensorimotor speed task[63] and a rotary pursuit task[61], preserved implicit learning in schizophrenia was demonstrated.

Given this background of absent or minor sensorimotor learning deficits in schizophrenia, our current finding of both explicit and implicit adaptation learning deficits is very interesting. Overall, this study suggests that sensorimotor learning during adaptation, which is impaired in schizophrenia, involves different processes than those required in the training of a sequence or sensorimotor skill, where only minor impairments were detected. This notion agrees with findings from Stark-Inbar et al.[38].

The present results of reduced adaptation in schizophrenia are in line with previous findings[155,169] supporting Andreasen's "cerebellar cognitive theory"[162–164]. Recent imaging studies pointing at dysfunctional cerebellar activation[26,27,150,165], decreased cerebellar-thalamic circuits[27], and decreased connectivity with the primary motor cortex[165,166,185] in schizophrenia support this theory.

Studies on adaptation in the ageing literature show diminished explicit strategic control in elderly individuals associated with age-related changes to the corticostriatal network. Implicit learning in a later automatization phase is relatively preserved in the elderly, and this has been linked to the only minimal degradation of the cortico-cerebellar system in ageing[57,58,186,187]. Results of the current study are not completely in line with these general findings as elderly individuals demonstrated significant adaptation differences compared with controls in only the vertical reversal task.

Results of the current study demonstrated that the rate and extent of adaptation of patients with schizophrenia was significantly reduced compared with the elderly. This was demonstrated in the gain adaptation and the vertical reversal tasks and occurred both during explicit and implicit stages of adaptation, even though the patients were equally hampered in baseline sensorimotor speed and outperformed the elderly in sensorimotor control on previously documented circle and figure pursuit tasks[68].

It must be noted that all patients with schizophrenia in the current study were taking (more than) one antipsychotic at the time of testing, which may partly explain their poor sensorimotor adaptation performance. As it is not known to what extent antipsychotics interfere with (general) sensorimotor function during a prolonged series of learning sessions[171], further studies should investigate the effect of different antipsychotics on adaptation learning.

A second limitation of the study is that only individuals who were able to complete the tasks were included in the study. As such, the sensorimotor adaptation abilities demonstrated in this study might be higher than what would be expected in schizophrenia. However, the number of negative symptoms (measured with the SANS rating scale) were comparable to a large heterogenous sample of patients with schizophrenia[113], suggesting that results of the current study may be reflective of general schizophrenia. Ultimately, task methodology differences hamper comparing results because they differ on several domains.

To conclude, patients with schizophrenia adapted less to perturbations than healthy controls on three sensorimotor adaptation tasks, regarding

both explicit and implicit learning. This finding adds to current evidence implicating the role of the cerebellum in the pathophysiology of schizophrenia. Also, sensorimotor adaptation was more impaired in schizophrenia than in the elderly, which challenges the accelerated ageing hypothesis of schizophrenia[51,52].While theoretical significance of the current results needs further research, practical implications for rehabilitation of patients with schizophrenia emerge. Patients with schizophrenia can adapt their common daily activities to changes in the environment. However, they have considerably more difficulty with it, and it takes them more time.

CHAPTER VII – IMPROVING MOTOR ACUITY AND CONTRASTING EXPLICIT MOTOR AND COGNITIVE LEARNING

Motor learning and performance in schizophrenia and aging: two different patterns of decline.

The results of this Chapter are published in:

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Motor learning and performance in schizophrenia and aging: two different patterns of decline.

INTRODUCTION

As described in Chapter I, there are six categories of learning tasks that have been put forth as main paradigms for motor learning[39]: 'sequence learning', 'adaptation', 'tracking', 'precision and motor speed improvement', 'coordination', and 'applied' tasks. Sequence learning has been documented in Chapter V, adaptation has been outlined in Chapter VI, tracking has been described in Chapter III, an example of an applied task is described in Chapter IV. In this Chapter, we tested motor precision and speed improvement with a Single Aiming Task and contrasted explicit motor sequence learning and verbal learning by using an Explicit Pattern Learning Task and the California Verbal Learning Task.

Single Aiming Task

The Single Aiming Task (SAT) assessed the enhancement of speed and accuracy in a simple movement. This task was designed following the classic Fitts task[188] using an index of difficulty based on the amplitude (A) and target width (W). In our study, participants executed individual movements where both the movement length (A) and the target diameter (W) were systematically manipulated. Conducting this brief task over three sessions enabled the evaluation of motor learning. Previous research on single line drawing has demonstrated that individuals with schizophrenia tend to move at a much slower pace than control participants[92,189–191]. However, the examination of speed and accuracy improvement through repetition has not been explored. Based on limited tracking study results, we hypothesized that motor learning in schizophrenia would not be impaired. Conversely, in the elderly, learning in fine motor tasks has been observed to be reduced[57,192,193], leading to the hypothesis that the elderly would exhibit less learning in this task.

Explicit pattern learning task

An explicit motor sequence learning task was also administered, known as the Explicit Pattern Learning Task (EPLT). In the EPLT, participants were provided with clear instructions that the targets were presented in an

unchanging, predetermined sequence, which they had to learn (refer to Figure 2). The subsequent target had to be discovered through trial and error.

Traditionally, the learning of a sequence of movements, sensorimotor adaptation, improved tracking performance, or enhanced motor speed and accuracy were categorized as procedural or implicit learning. Implicit learning was regarded as the automatic and unconscious acquisition of information, contrasting with declarative or explicit learning, which involves a deliberate intention to learn and necessitates conscious awareness. However, in recent decades, it has become increasingly evident that cognitive engagement plays a significant role even in so-called implicit learning paradigms like motor sequence learning and adaptation[37]. Nevertheless, if participants are explicitly informed that a sequence is learnable or if they are made aware of the necessity to adapt to specific changes in movement conditions, it markedly affects the learning rate. Available experimental evidence in this regard is limited and inconclusive[63–65,68]. Therefore, utilizing the EPLT allows for an exploration of the contrast between previously reported results of implicit sequence learning and an explicit form of the same type of motor learning.

Due to the known cognitive deficits in schizophrenia, it was expected that explicit learning in schizophrenia would be impaired, in contrast to implicit sequence learning. Furthermore, as the EPLT represents a more complex motor learning task than the SAT, elderly participants were anticipated to face greater challenges in mastering this task,[192] despite their preserved cognitive abilities. Another reason for anticipating lower EPLT learning in the elderly is based on reports of difficulties in simultaneously performing cognitive and motor tasks [194].

California Verbal Learning Test

To contrast the results of explicit motor learning with a measure of cognitive learning, we conducted the California Verbal Learning Test (CVLT). Verbal learning deficits have been well-documented in schizophrenia[195] and older age[196]. Therefore, it was anticipated that both experimental groups in this study would exhibit diminished verbal learning compared to the control group.

METHODS

Single-Aiming task

To acquaint themselves with the task equipment and design, participants underwent training using a single-aiming task. On the screen, four potential targets were displayed as open circles. In each trial, a cursor—a turquoise dot measuring 4 mm in diameter—appeared at the location of the previous target, marked by a solid yellow circle. The participants' instruction was to swiftly guide the cursor to the next target, which was indicated by a dark blue circle. A visible square border constrained the possible target locations to three circles (refer to Figure 1, left panel). The trial concluded when the cursor remained within the target circle for 100 milliseconds, signaled by a brief beep and a change in the target circle's color to yellow. Following an intertrial interval of 100-108 milliseconds, necessary for data storage, the subsequent trial commenced. The sequence of target locations was randomized.

Task complexity was manipulated by altering the distances between the circles (20mm versus 28.3mm diagonal or 40mm versus 56 diagonal) and varying the circle sizes (5mm versus 10mm). Combining these two manipulations resulted in four conditions of increasing difficulty (A to D). Each condition comprised 2 blocks of 10 trials, presented in an ABCDDCBA order. With ten practice trials included, this task, consisting of 90 trials, typically spanned 3 to 5 minutes.

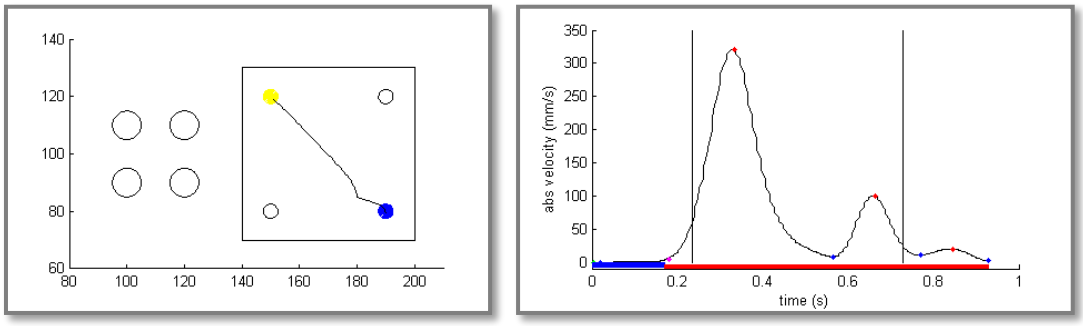

Figure 1. *Left panel:* Target display in the Single-Aiming task (on a 280 * 200 mm computer screen). Illustrated is an example of the cursor trajectory on a single trial of one participant. *Right panel:* Absolute velocity of the pen trajectory of the same participant. The two vertical lines denote the crossing of the border of the yellow starting circle and of the blue target.

Explicit Pattern Learning Task

The EPLT shared similarities with the IPLT; however, in the explicit version of the task, participants received clear instructions that the targets were presented in a fixed order they needed to learn. Unlike the IPLT, the next target was not indicated by a colored circle but had to be discovered through trial and error. Once the correct target was hit, it changed to turquoise, and after 100 milliseconds, it transitioned to yellow, indicating the need to find the next target. The target size (10 mm) and distance (20 mm or 28 mm) remained consistent with the IPLT. To minimize the influence of transfer from the implicit task, the task layout and target circle colors were altered (refer to Figure 2). In each trial, a square border confined the potential targets to three circles (see Figure 2). The lines of this square border became progressively thinner after every 60 trials and vanished after the 180th trial. Like the implicit task, the sequence to be learned consisted of 12 targets. Session 1 comprised five blocks of 60 trials, while sessions 2 and 3 each had 3 blocks of 60 trials.

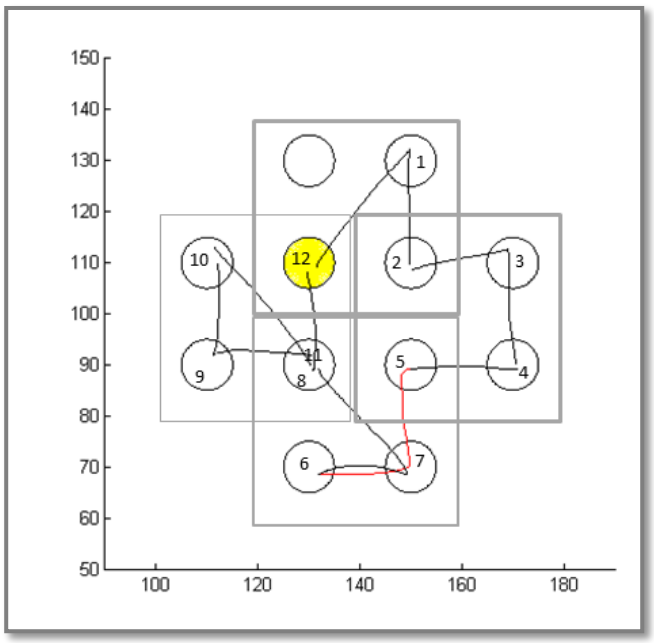

Figure 2. Layout of the targets display in the *EPLT* (open circles). On the first 180 trials, a grey square was displayed indicating that the choice for the next target was limited to the other three circles within the square. The four possible grey squares shown in this figure were never presented together. The sequence that had to be learned is indicated by ascending numbers (not shown to the participants). Illustrated is the cursor trajectory made by one participant in a set of 12 trials at the end of training. This participant made one error (shown in red); on its way from target 5 to 6, target 7 was touched first.

California Verbal Learning Test

The CVLT, a neuropsychological test designed to assess episodic verbal learning and memory, involves the oral presentation of a list of 16 words to participants on five occasions. Following each presentation, participants are immediately asked to recall as many words as they can (immediate recall; IR). After a 20–25-minute interval (delayed recall; DR), participants are once again tasked with reproducing as many words as they can from the original list. Following the DR phase, participants are presented with a list of 32 words and asked to identify the 16 words from the original test list (word recognition; RC).

During the second (Day 2) and third (Day 7) sessions, the original test list is not presented, meaning that only delayed recall and word recognition tests are administered, with no immediate recall test.

RESULTS

Single-Aiming Task

The Single-Aiming Task was modelled after the classic *Fitts task* (Fitts, 1954), which required participants to tap a stylus alternately between two targets. Fitts devised an index of difficulty (ID; Log2[2A/W]) to quantify these movements, considering the amplitude (A) and target width (W). In our study, participants executed a single movement with systematically varied movement lengths (20, 28, 40, or 56 mm) and target diameters (5 or 10 mm). According to Fitts' formula, the ID for these eight combinations ranged from 2.0 to 4.5. Two conditions yielded identical IDs: A=20, W=5 and A=40, W=10 (both with an ID of 3.0), as well as A=28, W=5 and A=56, W=10 (both with an ID of 3.5).

The mean movement time (MT) per group, averaged across sessions, for the eight possible conditions, is depicted against the index of difficulty in Figure 3. Straight lines fit these group means exceptionally well (with R2 values ranging from 0.987 to 0.994), and the two conditions with an ID of 3.0, as well as the two conditions with an ID of 3.5, resulted in nearly identical mean MTs in the patients and the elderly. It is noteworthy that the elderly and schizophrenia participants required significantly more time ($F(1,29) = 22.52$, $p = .0001$) in the ID=3.0 condition when the target was smaller (MT=0.493 s) compared to the conditions with a larger amplitude and wider target (MT=0.454 s).

Figure 3 also highlights notable group differences ($F(2,83) = 14.64$, $p < .0001$). In general, the control group demonstrated significantly faster MT compared to both individuals with schizophrenia and the elderly ($p < .0001$), with no significant difference between the schizophrenia and elderly groups ($p = .516$). The slopes of the linear trend lines for schizophrenia (0.216 s / ID) and elderly participants (0.214 s / ID) were significantly steeper than the slope of the trend line for the control group (0.184 s / ID). The linear interaction between ID and group reached significance ($F(2) = 6.61$, $p = .002$).

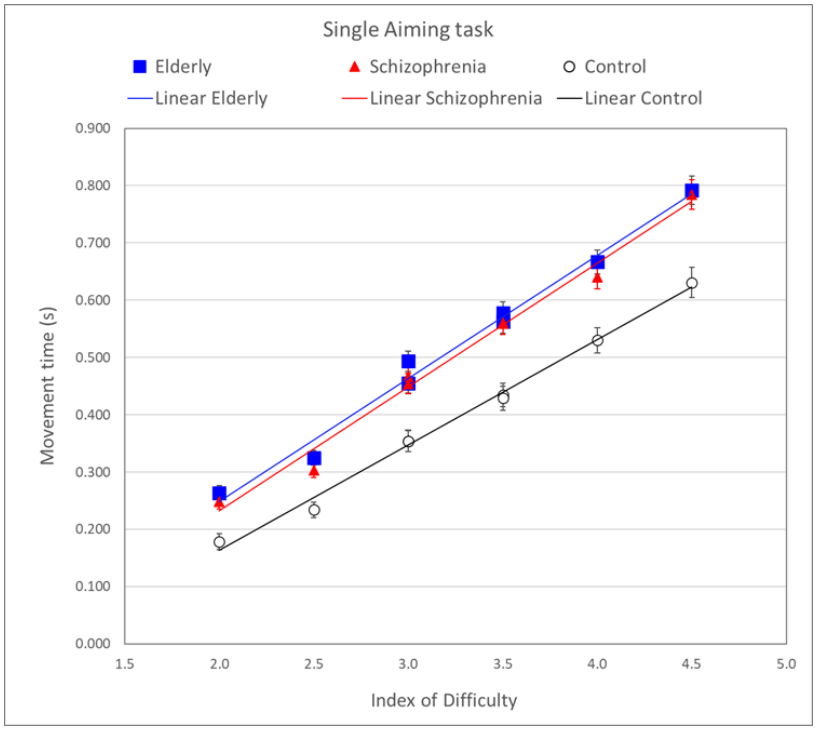

Figure 3. Mean movement time per group in the *Single-Aiming Task* averaged over sessions and displayed as a function of the 'Index of Difficulty' of the task conditions.

Despite the task's simplicity, all participants exhibited improved target-reaching speed over time. The mean MT for all eight conditions (as depicted in Figure 4, the leftmost panel) significantly decreased across sessions ($F(2,82) = 119.40$, $p < .0001$). This reduction was more pronounced for the elderly and schizophrenia groups in comparison to the control group, as evidenced by the significant group by session interaction ($F(4,164) = 4.48$, $p = .002$).

Despite the similarity in MT between schizophrenia and elderly participants, their movement kinematics exhibited significant distinctions. Most movements toward a target comprised a primary main movement, often followed by one or more corrective movements if the primary movement failed to reach the target (refer to Figure 1).

Elderly participants achieved the target with their primary movement in only 31% of trials, a lower rate ($p = .010$) compared to the 39% correct primary movements observed in both the schizophrenia and control groups (as seen in Figure 4, second panel). This was mirrored by the frequency of

additional corrective submovements (depicted in Figure 4, third panel), with elderly participants averaging 1.72, a significantly higher figure (p=.010) than that of the schizophrenia group (1.37) and the control group (1.29). In contrast, both individuals with schizophrenia and the elderly exhibited similar mean peak velocities (Figure 4, rightmost panel) (E: 142 mm/s, S: 138 mm/s, p=.589) and significantly differed (p<.0001) from the control group (C: 181 mm/s).

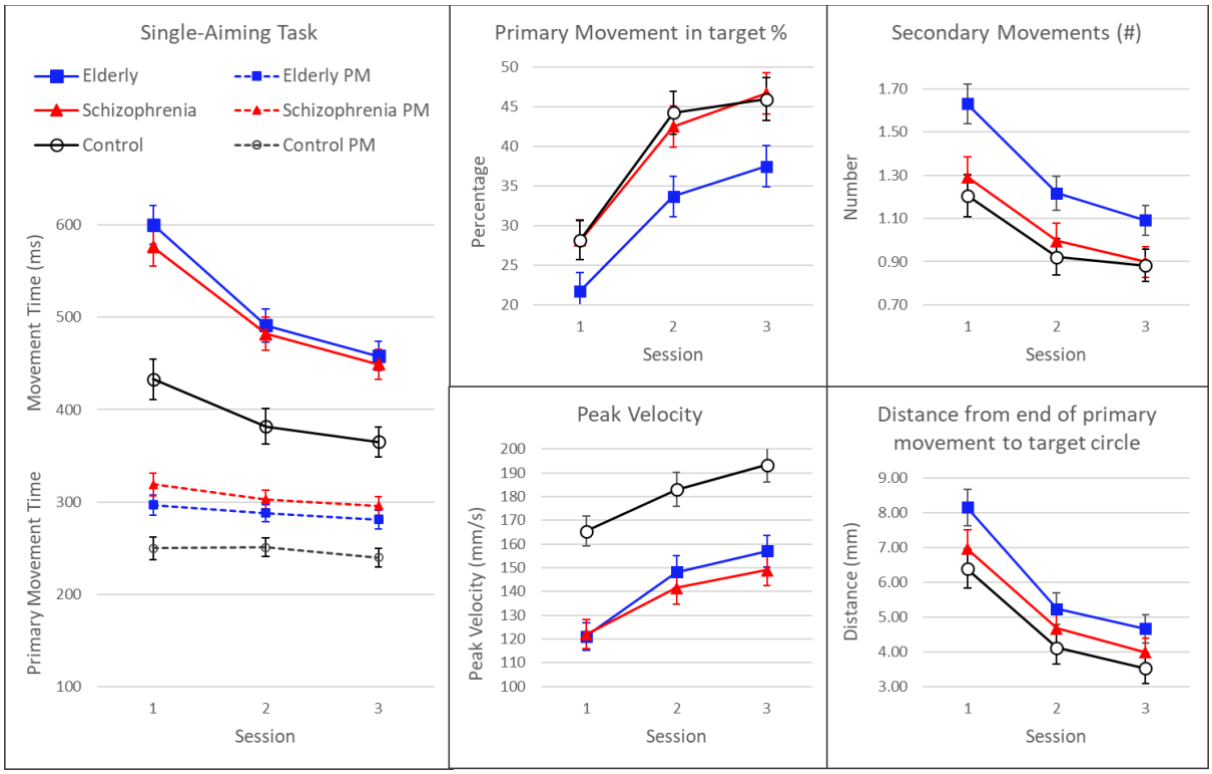

Figure 4. Left panel: mean movement time (MT) and mean movement time of the primary movement (PM MT) per group and per session in the *Single-Aiming Task* averaged over all 'difficulty' conditions. Additional panels: mean percentage of the primary movements ending in the target (PM in target), mean number of secondary / additional submovements (N Sec Moves), mean peak velocity (Peak Vel) and mean distance from the end of the primary movement to the target (EM distance) of the groups per session.

Explicit Pattern Learning Task (EPLT)

Total time to target - The explicit learning of a movement pattern can be best understood by examining the reduction in the total time required to reach the next target. This 'total time to target (TT),' which encompasses both reaction time (RT) and movement time (MT), was calculated by averaging data from 60 trials per block, equivalent to 5 complete twelve-trial patterns. The results for each group are presented in Figure 6. The figure reveals a substantial decrease in total time across the five blocks in session one ($F(4,83) = 86.70$, $p < .0001$), a pattern that was similar among the three groups (block*group interaction, $F(8,166) = 1.12$, $p = .355$). However, when considering the data averaged across blocks, significant differences between the groups emerged ($F(2,86) = 10.90$, $p < .0001$; elderly > schizophrenia: $p = .037$ and schizophrenia > control: $p = .014$). Over subsequent sessions, a further significant reduction in the total time to target was observed ($F(2,85) = 37.97$, $p < .0001$), and this trend was relatively uniform across the three groups (session*group interaction, $F(4,170) = 1.08$, $p = .369$). Notably, in this session-effect analysis, only data from the last three blocks of session 1 were considered. Once again, a significant reduction across blocks was evident ($F(2, 85) = 123.07$, $p < .0001$), and no significant group by block interaction was detected ($F(4,170) = 1328$, $p = .265$). Additionally, the groups differed significantly in the average total time to target ($F(2,86) = 17.08$, $p < .0001$; elderly > schizophrenia: $p = .002$ and schizophrenia > control: $p = .011$).

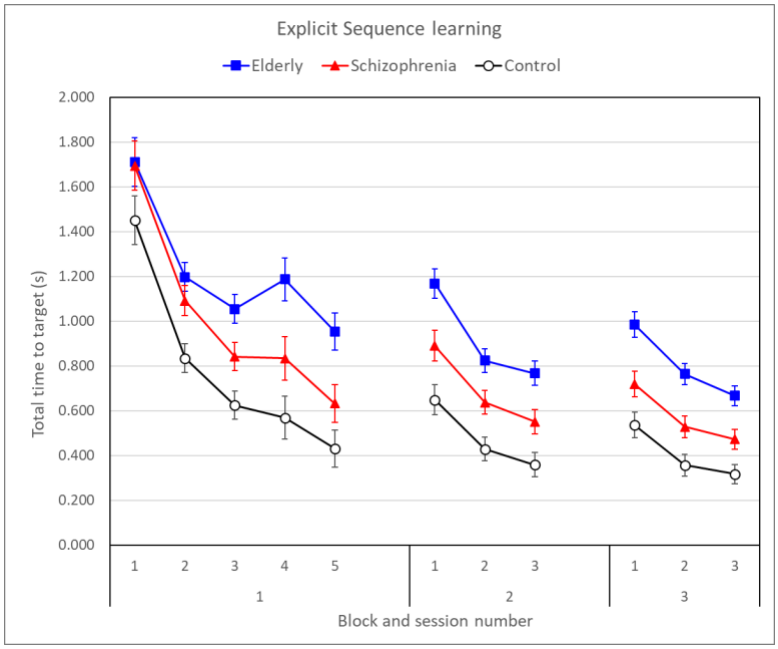

Figure 6. Total time to target in the Explicit Pattern Learning Task, averaged over 60-trial blocks per group.

Target errors - Group disparities in total time to target could be attributed to either slower learning or reduced sensorimotor speed. The number of target errors (as illustrated in Figure 7) provides a clear answer. An analysis incorporating the factors Session, Block (3), and Group yielded significant effects for session (F2, 85) =6.61, p=.002) and block (F (2,85) =22.11, p<.0001). Most notably, the group factor was significant (F2,86) =9.59, p=.0002), but this was primarily due to the elevated error rate among the elderly participants (elderly versus control: p=.0001, elderly versus schizophrenia: p=.001), while the contrast between the schizophrenia and control groups was not statistically significant (p=.549). This suggests that slower explicit pattern learning is primarily observed in the elderly group.

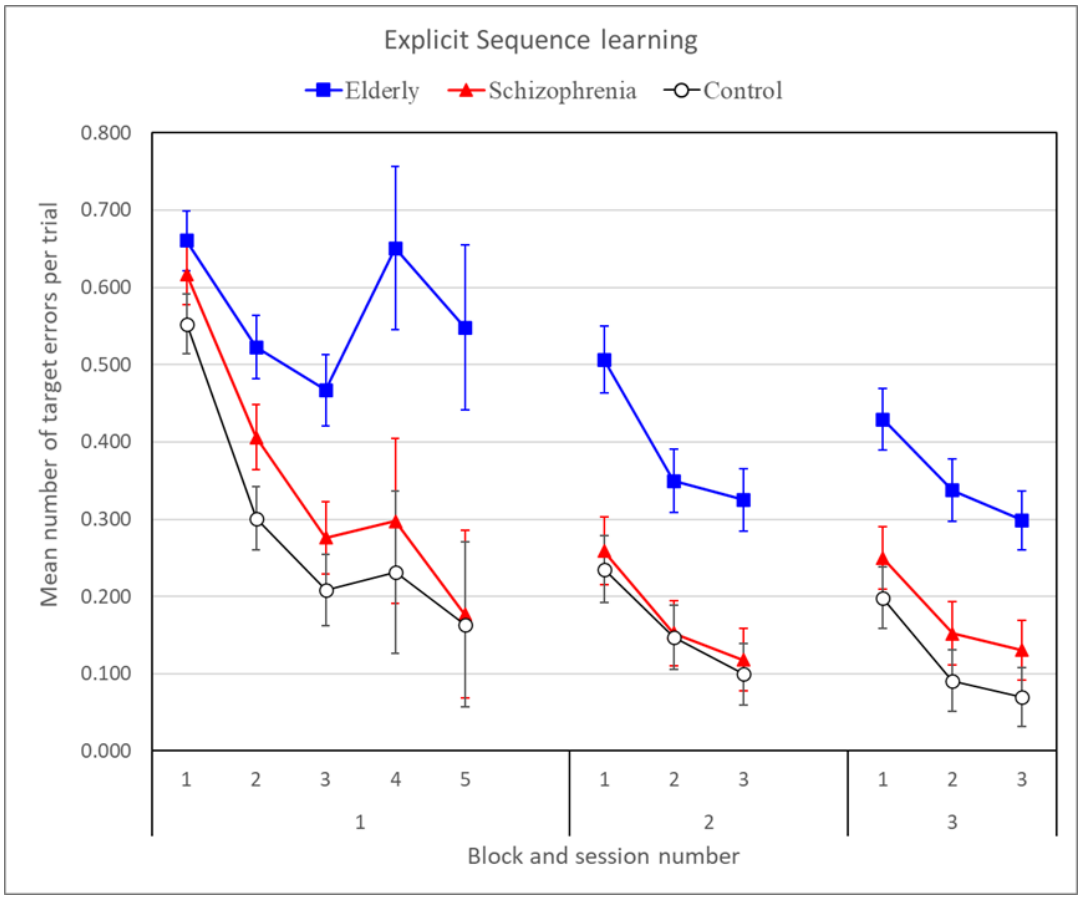

Figure 7. Mean number of target errors per trial in the Explicit Pattern Learning Task, averaged over 60-trial blocks per group.

Reaction time - Further support for this interpretation is obtained by splitting the total time to target into reaction time (RT) and movement time (MT). Both TT and MT are influenced by the additional time required for correcting target errors. Consequently, we also computed RT and MT exclusively for errorless trials.

MT on errorless trials was comparable between the elderly and schizophrenia patients (MT, E: 200, S: 211, C: 150ms), but RT was significantly longer in the elderly (p=.011) compared to patients and controls (RT, E: 368, S: 288, C: 212ms). To validate this finding, we calculated RT and MT on errorless trials in the implicit learning task (IPLT). In the IPLT, the RTs of the elderly and patient groups did not differ (RT, E: 263, S: 261, C: 207ms; MT, E: 245, S: 247, C: 191ms). Consequently, the notably prolonged RT of the elderly in the EPLT aligns with their lower MT scores and increased target errors only in explicit sequence learning.

California Verbal Learning Test (CVLT)

Immediate recall - As expected, and as depicted in Figure 5, the results of the immediate recall task revealed that all three groups exhibited episodic verbal learning. In general, there was a notable increase in the mean number of correctly recalled words immediately after presentation ($F(4,83) = 161.64$, $p < .0001$), and the pattern of recall across repetitions did not significantly differ between the groups (repetition * group: $F(8,166) = 1.73$, $p = .095$). However, when immediate recall scores were averaged across repetitions, significant differences emerged among the groups ($F(2,86) = 8.36$, $p = .0005$). These differences primarily stemmed from distinctions between schizophrenia patients and controls ($p < .001$) and between schizophrenia patients and elderly participants ($p = .019$). Importantly, the mean immediate recall of the elderly group did not significantly differ from that of the control group ($p = .095$). In other words, while all participants demonstrated learning over time, the schizophrenia group performed less proficiently than the other groups.

Delayed recall - It is entirely natural for word recall to decline over time and across sessions. The mean delayed recall (as shown in Figure 5, right panel) did indeed decrease ($F(2,85) = 11.30$, $p < .0001$), and the rate of this decline turned out to be notably distinct between the groups (session * group: $F(4,170) = 2.28$, $p = .038$). When delayed recall scores were averaged across

sessions, significant group disparities emerged as well (F (2,86) =7.08, p=.001). However, these group differences were already evident in the number of words learned after five repetitions. To account for this, we recalculated the delayed recall score as a percentage of the immediate recall score after the fifth repetition (DR%). While this adjustment did not alter the group by session interaction, it revealed that the schizophrenia group experienced the most significant decline in delayed recall after one week, from session 2 (Day 2) to session 3 (Day 7), in contrast to the elderly group, which demonstrated a reduction only from session 1 (Day 1) to session 2 (Day 2), after one day (Figure 5). However, the overall group differences were no longer statistically significant (F (2,86) =2.13, p=.125), except for session 3, where the control group outperformed (DR%=94%) the schizophrenia group (DR%=81%, p=.04) and the elderly group (DR=81%, p=.03).

Word recognition - The third variable assessed in this task, word recognition, yielded high group scores, ranging from 93% to 100% of the 16 words, and these scores were not significantly different (F (2,85) =1.22, p=.301).

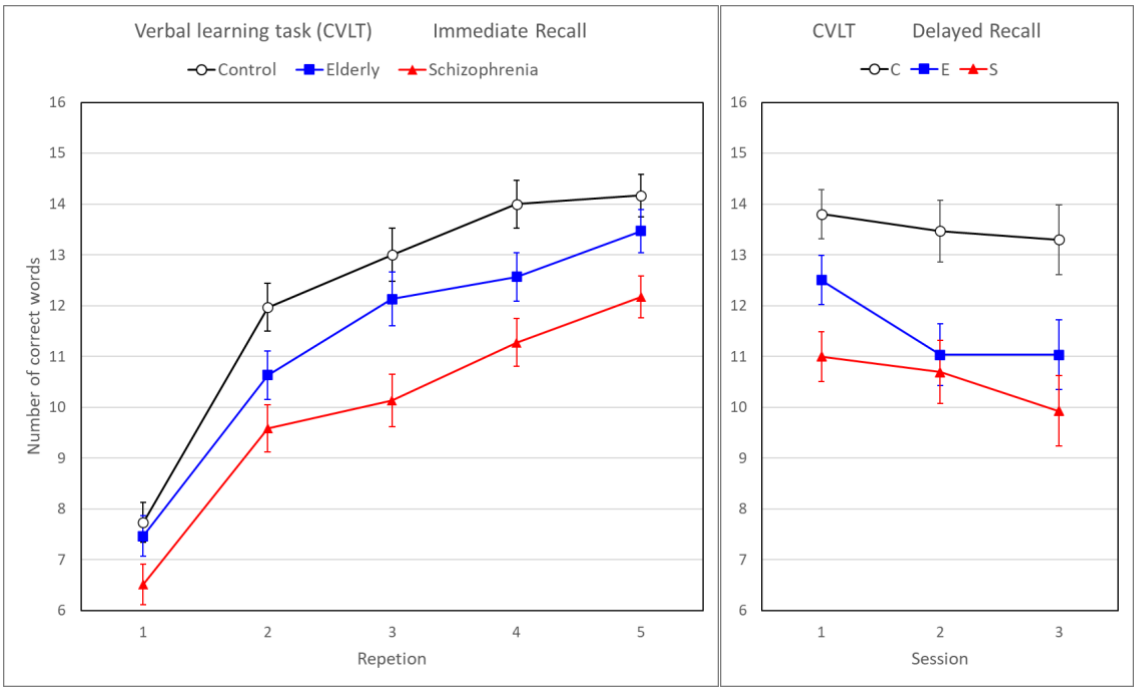

Figure 5. Mean number of correct words per group over repetitions in immediate recall (left panel) and over sessions in delayed recall (right panel).

DISCUSSION

Single-aiming task

The single-aiming task systematically manipulated movement difficulty by varying target size and target distance[188]. In line with Fitts' law, MT linearly increased with the task difficulty in all three groups, with the control group exhibiting significantly faster performance compared to both experimental groups.

While both individuals with schizophrenia and the elderly displayed similar MTs and peak velocities, elderly participants demonstrated less accuracy in their initial main movement, necessitating a higher number of additional corrective submovements. Additionally, when examining movement kinematics, it became evident that as movement difficulty increased, particularly when target size was halved or the distance to the target was doubled, elderly individuals had significantly longer MTs than controls, a contrast not observed in individuals with schizophrenia.

The underlying cause of this slowing among the elderly, as reflected by their extended MT, may stem from reduced movement precision or decreased movement speed. If there is greater variability in muscle force (indicating lower precision) during the execution of the primary movement, it can lead to more frequent target misses, necessitating additional corrective movements and resulting in prolonged movement times. This appears to be the case, as elderly participants required more corrective movements than individuals with schizophrenia, despite having similar peak velocities.

This finding and its interpretation align with previous research, which suggests that age-related slowing primarily arises from diminished movement accuracy[192] and increased movement variability[194], necessitating multiple corrective movements. Based on our data, it remains unclear whether this variability originates in the planning phase of the movement, the transmission of these plans by the peripheral nervous system, or the execution by the muscles.

We observed that many elderly participants frequently expressed surprise and frustration at their inaccuracy, which might have motivated them to exert extra effort in ensuring the corrective secondary submovements were

executed as swiftly as possible. This compensatory effort and the resultant patterns of heightened cortical activation in aging have been explored in prior studies.[197,198]

Explicit sequence learning task

The results from the explicit sequence learning task (EPLT) revealed that, once again, controls exhibited faster learning and achieved higher scores compared to both experimental groups. However, individuals with schizophrenia outperformed the elderly participants significantly on this task. The high rate of target errors among the elderly indicated significant difficulty in learning the sequence. Notably, their elevated error rate in the third session implies that elderly participants may not have correctly stored the target positions or encountered challenges in retrieving them.

One plausible explanation is that elderly individuals required additional attention to rectify their frequent movement inaccuracies. This heightened focus on correction might have limited their capacity for conscious encoding and retention of identified target positions.

Furthermore, it's possible that they were overly fixated on movement speed, adopting a similar strategy as in previous tasks (SAT, IPLT). This attention to speed could have interfered with their ability to simultaneously encode and retrieve target positions. Nevertheless, this explanation seems unlikely because it would imply that elderly participants didn't allocate sufficient time between trials to code and store target positions. Considering that trials followed one another with only a 100ms delay, the time for coding and storage is essentially a component of the reaction time (RT) for the subsequent trial. According to this explanation, the RT of the elderly group should have been smaller than that of the schizophrenia group. However, the opposite was observed, with significantly longer RT in elderly individuals compared to those with schizophrenia in the explicit sequence learning task, in contrast to similar RT in the implicit task. In other words, it appears that the actual process of explicitly learning the sequence of target positions may be impaired in the elderly.

California Verbal Learning Task

Patients and elderly individuals did not encounter difficulties with word recognition in the CVLT, but they did experience challenges with word recall.

In contrast to the results of the EPLT, elderly participants performed significantly better on the verbal learning task (CVLT), which is a cognitive task, compared to individuals with schizophrenia. In the CVLT, participants could fully concentrate on a single type of information, whereas the EPLT demanded additional attention for movement execution. Notably, the CVLT was not conducted under time constraints, and the 16 items to be remembered had simple word-based codes, whereas the EPLT required intricate spatial coding for the 12 target positions (e.g., 'move one step diagonally down to the left from your current position'). Therefore, the EPLT can be classified as a complex learning task, aligning with previous suggestions that motor learning diminishes in old age as tasks become more intricate [57,193].

CONCLUSION

These new findings underscore that there are differences in motor learning and performance between individuals with schizophrenia and the elderly across distinct motor learning tasks. The observed patterns of results over all learning tasks of the entire study within each group will be examined in Chapter VIII.

CHAPTER VIII – REVIEW AND DISCUSSION

MAIN FINDINGS

Our comprehensive investigation encompassed various sensorimotor subprocesses, including explicit and implicit sequence learning, adaptation, motor acuity, tracking, applied writing tasks, and cognitive assessments. In the following sections, we discussed the main results of each task that is elaborated in detail in the previous Chapters separately.

Table 1 provides an overview of group results per motor and cognitive learning task. The size of the differences between the schizophrenia group and the elderly group compared to the control group are expressed as *Glass's delta scores*. These scores are presented only when group differences reached statistical significance.

Subsequently, we compared and summarized these findings in order to pinpoint specific deficits in sensorimotor learning in schizophrenia and to draw comparisons between schizophrenia and senescence on sensorimotor learning and performance. A comparative overview of differences in performance and learning between all groups is provided in Table 2.

Single Aiming Task

There was a decrease in movement time in the elderly (24%), schizophrenia (22%) and control group (16%). This improvement was more pronounced in the elderly and schizophrenia groups, which could be attributed to their initially slower movement times. While it was expected that individuals with schizophrenia would not have difficulty learning in this task, the hypothesis that elderly participants would struggle with this type of learning was not confirmed. However, the control group reached the targets much faster and with a higher peak velocity in the main primary movement compared to both experimental groups.

The accuracy of the principal movement was significantly lower in the elderly group, leading to a higher frequency of secondary movements compared to the schizophrenia group.

When comparing conditions with an equal Index of Difficulty, there was a nearly perfect linear increase of movement times with task difficulty. However, the elderly deviated from this linear trend with longer movement times when the target was small. In other words, while the elderly

demonstrated significant learning, they exhibited a lower accuracy compared to individuals with schizophrenia.

Implicit Pattern Learning Task (IPLT)

The enhancement of acuity in sequence learning is evident through a reduction in the total time to target (TT) from trial block R1 to R2. Sequence learning becomes apparent from block L1 to L5. However, the most reliable measure of sequence learning is reflected in the difference in TT between blocks R2 and L5. The results clearly indicate that while both the elderly and schizophrenia groups were significantly slower than the control group (Table 1: Block R1 IPLT), there was no discernible difference in their degree of sequence learning on one test session and on a session one day later.

As patients with schizophrenia and elderly both displayed less explicit sequence recall, the control group superiority that became evident only after 1 week could be explained by an explicit learning component. The few patients with schizophrenia and elderly subjects who had some sequence recall could possibly utilize this explicit knowledge to improve their task performance but did this by distinct mechanisms.

Explicit Pattern Learning Task (EPLT)

As hypothesized, both individuals with schizophrenia and the elderly exhibited slower explicit sequence learning compared to controls. However, unexpectedly, the rate of learning in the elderly group was considerably lower than that of the schizophrenia group. The notably high frequency of target errors made by elderly participants, even into the third session, suggests potential difficulties in either storing or retrieving the target positions accurately. A plausible explanation for the difficulties in the elderly might be that they require additional attention to rectify their frequent movement inaccuracies. This heightened demand for attention might limit their capacity to consciously encode and store discovered target positions while in motion. If their primary goal was to quickly identify the correct target through trial and error and rely on automatic storage, they might not have dedicated sufficient attention and time to encode the specific features of each identified target. Consequently, the prolonged reaction time could be attributed to efforts to retrieve the location of the

next target from memory, which may not have been adequately stored earlier. In support of this explanation, numerous studies[194] have reported deficits in older adults when simultaneously performing cognitive and motor actions.

Rotation Adaptation Task and Gain Adaptation Task

The main dependent variables in this analysis were movement time and errors, specifically the initial direction error (rotation adaptation) or the magnitude of undershooting (gain adaptation). The ANOVA results for the mean MT during adaptation (blocks 1 – 4), the extent of aftereffects (MT of block N ('normal') minus block 4), and the MT during baseline are provided in Table 1.

These analyses reveal that patients exhibited poorer motor learning in both rotation and gain adaptation compared to controls. Furthermore, the post-adaptation aftereffects in the gain adaptation task strongly indicate impaired implicit adaptation learning in the schizophrenia group. There were no statistically significant differences between elderly and controls. It's worth noting that the mean baseline MT in the patient group was relatively long, around 400ms.

Vertical reversal task

The vertical reversal task was set up as a test for explicit adaptation learning. Table 1 provides the MT averages over the adaptation blocks and the baseline trials. The data clearly demonstrate that explicit adaptation was diminished in the elderly, and this reduction was even more pronounced in the schizophrenia group. During baseline trials, patients and elderly were not significantly different and were naturally slower than the controls. An aftereffect in post-adaptation trials was only evident in session 3 for the control group.

Circle and Figure Pursuit Tasks

The primary dependent variable was the accuracy with which the cursor had to be maintained within a moving target. As anticipated, the control group exhibited the highest level of performance, which was significantly superior to the accuracy of the schizophrenia group. Surprisingly, the

schizophrenia group achieved considerably greater accuracy than the elderly participants.

Symbol Digit Substitution Task (SDST)

The results demonstrate in all groups a significant ($p<.001$) reduction in matching time across five blocks, providing substantial evidence for cognitive learning of the symbol-digit combinations. As expected, writing time did not exhibit any significant changes over repetitions. The negative slope of matching time across blocks was calculated for every individual. It's worth noting that not all participants achieved a score of at least 5*9 matches (group S: 25, E: 28, C: 28), which accounts for the limited degrees of freedom (df of 75/78) in these analyses. The results of the slope analysis (Table 1) indicate that the degree of cognitive learning was comparable among the three groups. However, the mean performance (averaged over blocks) on the test exhibited significant group differences. Matching time for the schizophrenia group was considerably longer than that of elderly and controls, whereas writing time was the highest among the elderly and the lowest among the controls.

California Verbal Learning Task (CVLT)

Results from the CVLT confirmed the anticipated outcome that both the elderly and schizophrenia groups performed less proficiently than the control group. However, in contrast to the findings from the EPLT, elderly participants displayed significantly better performance on this cognitive task than individuals with schizophrenia.

It's worth noting that the CVLT allowed participants to solely focus on one type of information, whereas the EPLT necessitated additional attention to the execution of movements. Moreover, the CVLT was administered without time constraints, and the 16 items that needed to be remembered had straightforward word codes. In contrast, the EPLT demanded intricate spatial coding for the twelve target positions (e.g., 'move one step diagonally down to the left from here').

Consequently, the EPLT could be categorized as a more complex learning task than the CVLT, aligning with prior suggestions that (motor) learning tends to decline with age as tasks become more intricate.

Summary of the findings

A summary of all test results is presented in Table 1 and Table 2. ANOVAs on these data yielded significant group effects, many with extremely low p-values. Only two of the 21 analyses produced insignificant results, the most notable being the lack of any group difference in the first session of the implicit pattern learning task. On all other variables, individuals with schizophrenia exhibited lower performance levels than the control group. The only exception was the improvement in acuity during motor learning in the SAT, where both patients and the elderly outperformed the controls (expressed as negative values). This deviation can be attributed to their exceptionally slow sensorimotor performance on this task, which yielded the highest Glass's delta score.

A more varied picture emerges when comparing the schizophrenia group with the elderly group. The elderly performed as poorly as the schizophrenia group on 9 of the 21 variables. However, on 3 of the 4 cognitive tests, the elderly group scored significantly better than the schizophrenia group, and the elderly group also outperformed the schizophrenia group on 4 of the 5 adaptation measures. On the other hand, on tasks requiring fine motor control, such as writing digits and tracking a moving cursor in pursuit tasks, the elderly volunteers performed significantly worse than the schizophrenia patients. An intriguing contrast is also provided by the scores of the elderly on the explicit verbal and motor learning tasks: On the verbal learning test, the elderly performed not different than the controls and scored much better than the schizophrenia group, but on the explicit pattern learning task, the elderly group performed remarkably inferior to the patients and the controls.

The findings of this investigation demonstrated significant learning in patients with schizophrenia and in elderly individuals in all categories (except in the over-learned task of writing digits). These learning results were obtained despite marked psychomotor slowing in both groups, as evidenced by slower movement times than controls on baseline trials in the explicit and implicit sequence learning tasks, adaptation tasks, and the single aiming task.

Importantly, our investigation revealed distinct patterns of reduced abilities between the two experimental groups. Specifically, the elderly

performed worse on tasks requiring fine motor control, such as tracking, writing numbers in the SDST and explicit sequence learning. Individuals with schizophrenia performed worse on motor adaptation and on most of tests that require more explicit, cognitive capacities, including the California Verbal Learning Task. These patterns will be further discussed separately below.

Table 1. Summary of test and task results on first session.

	Group effect in ANOVA's			**Group means**			**Glass's delta**		**Group contrasts**	
	F	df	p	Controls	Schizophrenia	Elderly	CS [1)]	CE [2)]	ES [3)]	SE [4)]
Motor Learning										
Improving acuity SAT (ms)	9.83	2,83	<.001	68	127	142	-1.28	-1.59		
Sequence Learning IPLT (ms)	0.28	2,86	.754	52	51	46				
Sequence Learning EPLT (ms)	10.90	2,86	<.001	781	1020	1222	.89	1.65		.037
Adaptation Rotation MT (ms)	5.16	2,85	.008	185	248	193	1.08		.011	
Adaptation Gain MT (ms)	7.75	2,83	.001	50	115	59	1.05		.002	
Adaptation Reversal MT (ms)	11.31	2,86	<.001	544	1041	829	1.67	.96	.046	
Tracking Circle (accuracy)	20.17	2,87	<.001	47	38	26	.69	1.64		<.001
Tracking Figure (accuracy)	24.58	2,87	<.001	59	50	33	1.11	2.57		<.001
Aftereffects										
Adaptation Rotation (ms)	1.28	2,85	.283	84	40	50				
Adaptation Gain (ms)	8.08	2,83	.001	78	-14	47	1.03		.010	
Sensorimotor performance										
SDST writing time (ms)	29.58	2,87	<.001	415	501	599	1.14	2.43		<.001
Single Aiming Task MT (ms)	17.87	2,83	<.001	433	576	601	2.98	3.49		
Block R1 IPLT TT (ms)	21.20	2,86	<.001	480	610	627	2.02	2.28		
Baseline AdapR MT (ms)	4.47	2,85	.014	320	405	402	1.23	1.18		
Baseline AdapG MT (ms)	7.01	2,83	.002	283	383	369	1.86	1.60		
VRT baseline MT (ms)	9.92	2,86	<.001	193	262	266	1.75	1.87		
Cognitive Learning										
SDST matching time (slope)	0.52	2,78	.597	-.039	-.037	-.055				
CVLT IR (Nwords)	8.36	2,86	.005	12.2	9.9	11.2	1.31	.54	.019	

Cognitive performance										
WCST categories (N)	5.79	2,84	.004	4.0	3.00	2.6	.65	.91		
LNS (Adj score)	10.29	2,86	<.001	9.7	7.2	11.2	.70	-.46	<.001	
SDST matching time (s)	13.46	2,87	<.001	.99	1.44	1.10	1.89	.43	<.001	

[1)] positive values denote lower learning or performance of group S compared to group C,
[2)] positive values denote lower learning or performance of group E compared to group C,
[3)] p values (Bonferroni corrected) denote lower learning or performance of group S compared to group E,
[4)] p values (Bonferroni corrected) denote lower learning or performance of group E compared to group S.

Table 2. Summary of findings: group comparisons

Motor Learning	**Task**	**Result**	**E vs S**
Improving acuity	SAT	Equal learning in C S E	
	IPLT (R1-R2)	Equal learning in C S E	
Sequence learning	IPLT	Equal learning in C S E	
	EPLT	Retarded learning only in E	S better than E
Adaptation	Rotation adaptation	Retarded learning only in S	E better than S
	Gain adaptation	Retarded learning only in S	E better than S
	VRT	Retarded learning in S and E	E better than S
Tracking	Pursuit circle	Retarded learning in S and E	S better than E
+ sequence	Pursuit figure	Retarded learning in S and E	S better than E
Applied (writing)	SDST writing	No learning	
Motor performance			
SDST writing		Psychomotor slowing in S and E	S better than E
Single-Aiming Task		Psychomotor slowing, equal in S and E	
Baseline MT		Psychomotor slowing, equal in S and E	
Cognitive Learning			
Symbol-digit associations	SDST matching	Equal learning in C S E	
Verbal learning	CVLT	Retarded learning in S and E	E better than S

C: controls; E: elderly individuals; S: patients with schizophrenia

MOTOR LEARNING IN SCHIZOPHRENIA

Individuals with schizophrenia demonstrated intact performance and learning on simple motor tasks, such as the single aiming task, SDST matching times and in the random blocks of the implicit learning task.

However, when conscious cognitive processing was required, as in the EPLT, the rate of learning in the schizophrenia group was significantly reduced compared to controls. This finding aligns with their reduced performance in the CVLT, a cognitive learning task, where individuals with schizophrenia performed worse than both controls and the elderly, underscoring their cognitive difficulties. Another manifestation of this cognitive deficit impacting motor learning tasks was observed in the IPLT, where patients displayed significantly less subjective sequence awareness. Therefore, it can be suggested that individuals with schizophrenia are impaired in sensorimotor learning paradigms in which explicit cognitive processes play a significant role.

However, in addition to the sometimes-minor effects of deficient explicit cognitive processing on learning in schizophrenia, their slower adaptation in the three adaptation tasks is more remarkable (see Table 1 and 2). They might have detected the perturbation of the movement later, but even in the last adaptation trials, they still lagged far behind the elderly and the controls in adjusting their movements to the altered sensory feedback. Even more revealing was their behaviour on post-adaptation trials, specifically in the gain adaptation and the vertical reversal task, which indicated that they had not changed an automatized forward model for movements in the altered situation, a model that needed to be corrected when normal feedback was again restored. Visuomotor adaptation is now generally viewed as the combined action of explicit learning driven by the detection of a performance error and implicit learning of a forward model driven by prediction error[199]. The significant difference in behaviour on post-adaptation trials of the schizophrenia group compared to controls and the elderly suggests that implicit sensorimotor adaptation in schizophrenia is also impaired. The implications of difficulties in motor adaptation in schizophrenia may suggest a general disability to adapt to changes in any situation, indicating a potential avenue for further research.

Cognitive and motor influences on motor slowing in schizophrenia

Understanding the nature of motor slowing observed in schizophrenia is essential, and it's crucial to emphasize the role of reduced cognitive processes related to motor slowing. These cognitive processes are quite broad and diverse, ranging from sensory processing to response selection, movement planning, motor execution and movement monitoring.

At a low level of cognitive processing, sensory processing (both auditory and visual) has been demonstrated to be dysfunctional in schizophrenia and found to contribute to higher-order cognitive dysfunction[201]. Sensory discrimination has also been found to be significantly lower in individuals with schizophrenia[202].

In addition, higher order perceptual processes have also been demonstrated to be deficient in schizophrenia. This was repeatedly demonstrated in studies using drawing tasks in which letters, familiar figures and unfamiliar patterns had to be copied[20,189,191,203,204]. Copying rests on cognitive processes such as recognition, coding, storage in working memory and subsequent retrieval of the figure that must be drawn. It also requires the use of executive processes to plan the optimal movement sequence.

Slowing in schizophrenia may also arise from an executive process that comes into play after movement initiation, viz the monitoring of the ongoing movement and any resulting movement corrections after detection of a mismatch between the (feedforward) model of the movement and the actual produced movement. In view of the previously mentioned deficiencies in sensory processing and sensory discrimination in schizophrenia[201,202], it is quite plausible that individuals with schizophrenia were less accurate or later to detect deviations from their planned movement. In addition, they might have been slower in making necessary movement adjustments. Monitoring and quick correction require intensive focused attention and sufficient arousal, which also might have been suboptimal in the schizophrenia group.

In a recent review on psychomotor slowing in schizophrenia, Osborne et al.[15] made a distinction between cognitive (prefix “psycho”) and motor execution (root word “motor”) aspects of psychomotor slowing. Motor

aspects were defined as processes implicated in the initiation, coordination, and execution of movements. Many studies have demonstrated that individuals with schizophrenia have impaired cognitive processes involved in response selection and motor preparation, however findings of impaired motor execution are less consistent[33]. Following this, the single-aiming task (SAT) and line copying tasks are a step towards investigating 'pure' motor execution aspects of sensorimotor slowing as these tasks require minimal cognitive processes. The present thesis therefore provides strong evidence for 'motor' slowing in schizophrenia (which is evident with very large effect sizes). This evidence is consistent with previously reviewed slow movements in the line-copying task[11,189–191,205,206], the slow movement times found in the baseline of our IPLT, VRT, SAT and adaptation tasks. Though the SAT has the least cognitive components compared with other tasks, this task still required some implicit planning involving the choice for the optimal posture of arm, hand and fingers. Similarly, drawing a single line (LCT) follows several implicit planning rules or so-called graphic production rules about the best way to start and to connect lines[207]. A vertical line is usually drawn from top to bottom. However, when drawing a series of lines that gradually tilt from vertical to horizontal, then somewhere halfway in that series most people change their movement direction from top-down to left-right. Individuals with recent-onset schizophrenia made this shift much less frequently or much later than healthy controls[203] suggesting that changing this implicit movement planning was more difficult in schizophrenia. In addition, when individuals with schizophrenia were instructed to begin drawing at a point that conflicted with the preference predicted by graphic production rules, more time was needed to initiate the drawing[203,208]. Together these results show that implicit planning of very simple movements is also affected in schizophrenia. Implicit planning of a movement, such as selection and positioning of our limbs is done without awareness of the choices or the forces that are involved. Yet it is based on 'knowledge', and the fact that a strong learning effect was demonstrated over sessions in these tasks suggests that this 'knowledge' can be increased. Therefore, it is hard to draw a cut-off between 'psycho' and 'motor' in action research, on a scale between pure motor execution and higher order cognitive processes[209,210].

Correlations of motor learning variables with schizophrenia symptoms

The correlations of all variables listed in Tables 1 and 2 with symptom severity (assessed with the Scale for the Assessment of Negative Symptoms and Positive Symptoms (SANS-SAPS)), are presented in Table 3.

Large standard deviations of SANS and SAPS scores made it clear that the group of participants with schizophrenia was far from homogeneous. SANS and SAPS scores were only modestly correlated with each other (0.33) and their correlations with the cognitive and motor variables were quite diverse.

Negative symptoms were associated ($0.42 < rho < 0.62$) with larger movement times on some simple motor tasks (LCT, SAT, adaptation tasks during baseline) but not on all of them. Therefore, the interpretation of the correlations of task performance with negative symptoms is not clear.

On the other hand, positive symptoms provide a more comprehensible picture. These data seem to point out that patients with more positive symptoms demonstrated inferior adaptation and lower set shifting ability (exhibited in WCST scores). In order to correct for multiple testing, we also indicated which correlations were significant at the 0.01 level (**). However, these results should still be interpreted with some caution: the findings that were found significant might be false positives. For example, the patients with high SAPS scores might have been extremely slow and rigid which might also influence their performance on Adaptation tasks. Replication in future studies is needed to ensure the reliability of these findings.

Table 3. Correlations (Spearman's rho) of test results with SANS and SAPS scores.

Symptom severity		SANS	SAPS
SANS	SANS	1.000	0.331*
SAPS	SAPS	0.331*	1.000
Cognitive tests			
WCST categories completed	WCST	-0.364*	-0.430**
Letter Number Sequencing	LNS	-0.360*	-0.149
California Verbal Learning Test IR	CVLT	0.112	-0.120
SDST matching time	SDSTmt	0.311	0.292
Sensorimotor tests			
SDST writing time (ms)	SDSTwt	-0.176	0.052
Line-Copying Task MT (ms)	LCT	0.427*	0.260
Single-Aiming Task MT (ms)	SAT	0.446**	0.207
Circle Pursuit Task (accuracy)	PursuitC	-0.106	-0.266
Figure Pursuit Task (accuracy)	PursuitF	-0.442**	-0.360*
Baseline MT (ms)			
Implicit Pattern Learning Task	IPLTbase	0.317	0.212
Vertical Reversal Task	VRTbase	0.231	0.252
Rotation Adaptation Task	AdapRbase	0.539**	0.496**
Gain Adaptation Task	AdapSbase	0.620**	0.405*
Learning blocks mean MT (ms)			
Implicit Pattern Learning Task	IPLT	0.389*	0.255
Explicit Pattern Learning Task	EPLT	0.494**	0.182
Vertical Reversal Task	VRT	0.300	0.460**
Rotation Adaptation Task	AdapR	-0.061	0.205
Gain Adaptation Task	AdapS	0.505**	0.369*
Implicit Learning aftereffects (ms)			
Implicit Pattern Learning Task (L5-R2)	IPLTafter	0 222	0.151
Rotation Adaptation Task (Block 4-N)	AdapRafter	-0.207	-0.348*
Gain Adaptation Task (Block 4-N)	AdapSafter	-0.262	-0.366*

* Correlation is significant at the 0.05 level (1-tailed).

** Correlation is significant at the 0.01 level (1-tailed)

MOTOR LEARNING IN THE ELDERLY

The elderly participants showed intact motor learning abilities when engaged in straightforward tasks, as observed on the single aiming task, random blocks of the IPLT and the baseline blocks of the VRT. These tasks were characterized by their simplicity, involving only short, swift, and straight movements directed towards clearly visible targets.

However, when confronted with tracking tasks that required closely monitoring a moving target, the elderly group exhibited notably diminished learning outcomes compared to both control groups and even the schizophrenia group[68]. Furthermore, the results of the current thesis revealed that elderly individuals encountered greater difficulty when explicitly attempting to learn a target sequence.

Our results show that adaptation seems to be relatively preserved in the elderly. Successful adaptation found in the elderly might arise because they constantly must deal with a variable, unreliable and unpredictable motor output system[200] which could make them more alert to deviations from an intended trajectory. They had possibly detected the perturbations earlier than the schizophrenia patients and might have developed earlier a cognitive strategy to counter the distortions in movement direction or amplitude. Similarly, in the vertical reversal task which asked for an even larger adaptation of the planning of a movement, elderly participants adapted faster than schizophrenia patients. Seidler and Carson[49] suggested that explicit cognitive strategies may be used to start adaptation from the very first trials, which might explain the relatively fast adaptation seen in elderly participants. Another possible explanation why the elderly performed better at adaptation tasks in contrast to sequence learning, might be because they only had to focus on the motor aspects of the task. Ultimately, older adults tend to rely more on visual feedback for motor control, which could explain why they displayed minimal disruption when faced with unexpected alterations, such as rotation or shortening of visual feedback during adaptation tasks. Online correction, driven by visual feedback, might have become an ingrained aspect of their general motor control strategy.

These combined findings align with the conclusions drawn in a frequently cited review by Voelcker-Rehage[192], indicating that age-related learning disparities become more pronounced in tasks of greater complexity and heightened difficulty. The 'complexity' or 'difficulty' of a task can be elevated in different ways. Firstly, this can be achieved by imposing additional demands on corrective motor control, such as reducing target size or altering trajectory paths[193], or by introducing moving targets that had to be monitored. Secondly, complexity increases when explicit cognitive processes required for planning or executing movement sequences necessitate more intricate processing, for instance, when sequences are longer or when the spatial coding of targets becomes more intricate. A third way of increasing complexity is when both increased demands on motor control and cognitive processing must be combined. In this thesis, all three types of complexity seem to make motor learning more difficult for the elderly. A comprehensive account of why 'complexity' leads to reduced motor learning in aging is provided by Seidler's 'Supply and Demand' framework[50,194]. According to this framework, age-related deficits in motor performance, including heightened movement variability and reduced speed, stem from dysfunction in the central and peripheral nervous systems, as well as the neuromuscular system. This motor deficit, indicative of a decreased supply of motor control, subsequently places greater demands on cognitive brain processes essential for motor control. As a result, the capacity for cognitive learning of target sequences is diminished.

RELEVANCE OF OUR FINDINGS AND FUTURE DIRECTIONS IN SCHIZOPHRENIA

Scientific relevance

The findings from this thesis contribute significantly to the scientific understanding of motor learning deficits in schizophrenia. While cognitive deficits have been extensively studied in schizophrenia, motor learning has received relatively less attention. This research bridges this gap by exploring the intricate relationship between cognitive processes and motor skills. As mentioned earlier, a wide range of distinct cognitive processes are intricately linked to motor slowing and reduced motor learning in individuals with schizophrenia. It has been postulated that the neural foundations of these processes involve parieto-frontal networks, the supplementary motor area (SMA), and the pre-supplementary motor area (pre-SMA), which play a crucial role in planning movement sequences[28,33]. This perspective has been expanded upon to incorporate the influence of biochemical modulation, particularly considering the interplay between affective changes and psychomotor mechanisms, which contribute to abnormalities in motor functioning[28]. In this broader view, the interaction between the 'psycho' and 'motor' aspects is emphasized, and the rigid separation of motor function from affective and cognitive functions is rejected. The challenges encountered in sensorimotor adaptation among individuals with schizophrenia serve also as compelling evidence for the interconnection of these various functions at a neurobiological level. Sensorimotor adaptation is heavily reliant on cerebellar activity, as demonstrated by previous research[37,41,194,211]. An influential integrative theory of schizophrenia, initially proposed by Andreasen et al.[163,212], presents the cognitive dysmetria model. This model posits that a disruption within the cortico-cerebellar-thalamic-cortical circuit underlies a wide spectrum of sensorimotor and cognitive dysfunctions. Within this circuit, the cerebellum assumes a pivotal coordinating role. One way to put this theory to the test is by investigating whether adaptation in individuals with schizophrenia is impaired, as explored in the study in Chapter VI. Furthermore, more recent work by Mittal et al.[27] underscores the significance of the cerebellum and the cerebello-thalamo-cortical-cerebellar (CTCC) circuits in psychomotor activity. This perspective aligns with

neuroimaging studies that have identified CTCC dysfunction as a contributing factor to sensorimotor abnormalities in schizophrenia[16,24]. The findings of 'motor' slowing and impaired implicit sensorimotor adaptation documented in this thesis, strongly support the notion of CTCC dysfunction in schizophrenia. This region might be of interest in future neuroimaging studies.

In addition, psychomotor slowing is not a unitary phenomenon, but consists of a wide range of distinct sub-processes of specific cognitive and motor deficiencies with possible different patterns across individual patients. This has important implications for future research. Clearly making a distinction between 'psycho' and 'motor' components is not only difficult but is also simplifying and masking the variety of possible delays in sensorimotor learning and performance. On the other hand, while it is valuable to stress the interconnectedness of cognitive and motor processes, treating psychomotor slowing in schizophrenia, depression and Parkinson's disease as a uniform dimension could detract from the goal to find the underlying causes of the motor abnormalities in these illnesses, which are probably highly different. Therefore, as a supplement to the extensive research on cognitive impairments in schizophrenia, which has led to the identification of separable cognitive factors in schizophrenia, future research should be conducted in the motor domain (in a RDoC perspective) focusing on distinct subprocesses contributing to psychomotor slowing in schizophrenia.

One of the aims of this investigation was to compare supposed declines in categories of motor learning in schizophrenia with expected decreases in the elderly. This was motivated by recent research of Kirkpatrick et al.[51,106], supporting the theory that schizophrenia might be a neurodegenerative disorder with genetic, functional-organic and neuroanatomical features of accelerated aging sharing similarities with elderly individuals. However, the results of the present thesis demonstrating different patterns of decline in motor performance and learning in schizophrenia patients and the elderly do not support this hypothesis.

Clinical relevance

The findings of this thesis have clinical implications as well. Daily functioning relies heavily on the quality of a range of cognitive abilities and motor skills. Both individuals with schizophrenia and their therapists must realise that both cognitive and motor symptoms influence the functional outcome in schizophrenia and that cognitive processes play a larger role in motor skills than previously anticipated, and it is difficult to disentangle. Motor performance and learning deficits in schizophrenia become more apparent with increasing cognitive task demands but difficulties also manifest in very simple motor tasks. These deficits have a large impact on daily functioning in work and home situations. Variability found amongst patients, suggests that psychomotor slowing may not be an obstacle for all patients. This prompts the use of diagnostic testing of motor skills to better understand the individual limitations which might be useful in the advice towards employment opportunities. The finding that significant motor learning is possible in schizophrenia might be of importance for rehabilitation programs in which motor skills are trained (i.e., sport, music or other leisure activities). It is also important to specifically focus on the adaptation difficulties in patients with schizophrenia during training programs.

LIMITATIONS

A few strengths and weaknesses of this large-scale investigation should be mentioned. Its strength lies in the design of the investigation in which multiple motor learning tasks were studied on the same set of participants and over repeated sessions. This might have created a limitation in that only individuals who were able to complete the tasks in all three one-hour sessions were included in the study. As such, the motor learning and performance capabilities demonstrated in this thesis might be higher than what would be expected in schizophrenia and at old age respectively. However, the mean and range of the scores on the negative symptoms scale (SANS) of the patients in the present study were comparable to a large heterogenous sample of patients with schizophrenia[213], suggesting that results of this thesis may be reflective of general schizophrenia.

A second limitation concerns the fact that all patients with schizophrenia in the current study were taking (more than) one antipsychotic at the time of testing, The effect antipsychotics on motor learning has still to be investigated.

It is possible that movement slowing in schizophrenia could be the result of sedentary lifestyles as opposed to neurological factors. Studies using actigraphy on patients with schizophrenia[214] showed that low physical activity and sedentary behaviour of many of these patients is associated with movement disorders, in particular slowing evident in parkinsonism. However, the patients in our study were out-patients and the elderly made a rather active impression on the evaluation clinician. More research is needed to determine whether psychomotor slowing leads to sedentary behaviour or whether an inactive lifestyle results in observed psychomotor slowing.

Another limitation is related to the correction for multiple testing. Although this thesis did not have an exploratory nature, as we primarily focused on comparing motor performance and learning for each learning task separately and applied Bonferroni correction to account for multiple comparisons when comparing elderly and patients, we have presented the results of the various tasks side by side in Table 1 (Discussion). Although the p-values are extremely low, the critical value of $p < 0.05$ might not be

enough to suggest significance. Also, in the interpretation of the correlations of motor performance with SANS and SAPS scores, caution is warranted. Significant correlations do not establish causation. These findings should be considered preliminary and replication in future studies is imperative to ensure the reliability of these findings. Additional research is needed to further explore the intricate relationships between motor performance, learning abilities, and symptomatology in schizophrenia, as our thesis serves as an initial step in this direction.

CONCLUSION

The first objective of this thesis was to measure and contrast motor learning and performance on various motor task paradigms in schizophrenia. We found that patients with schizophrenia did demonstrate motor slowing, but motor learning was significant, especially on simple motor tasks which required less explicit processes (such as strategy planning).

A second objective was to further investigate the role of implicit and explicit processes in motor learning tasks. This thesis clearly demonstrated that motor slowing is not a uniform phenomenon, rather it consists of a range of specific cognitive and implicit subprocesses. In general, patients with schizophrenia exhibited more difficulties in sensorimotor learning paradigms where explicit processes play a larger role. Importantly, patients exhibit difficulties in the implicit processes of motor adaptation, which supports the theory that the cerebello-thalamo-cortical-cerebellar circuit is disrupted in schizophrenia.

Third, this thesis investigated the similarities and differences between motor and cognitive functioning in schizophrenia and normal ageing. Our data clearly demonstrated a different pattern of decline, which challenges the accelerated ageing hypothesis of schizophrenia. Both groups exhibited psychomotor slowing, however both groups showed considerable motor learning. The differences were apparent by impaired adaptation in schizophrenia and reduced explicit motor sequence learning in the elderly. While motor slowing in schizophrenia appears to be caused by implicit planning deficits, slowing in the elderly may be caused by less accurate movement precision. Importantly, cognitive deficits seem to interfere with motor learning in schizophrenia and task complexity interferes with motor learning in the elderly.

Our fourth objective was to explore the degree to which specific motor behavior deficits are linked to both positive and negative symptoms in this disorder. The interpretation from the SANS and SAPS scores indicated that our group of patients was heterogenous. The interpretation of the correlations of task performance with negative symptoms is not clear. The correlations of task performance with positive symptoms, on the other

hand, seem to demonstrate that patients with more positive symptoms demonstrated inferior adaptation and lower set shifting ability. However, replication in future studies is necessary to ensure the reliability of these findings.

CHAPTER IX - SUMMARY

Schizophrenia is a severe disorder that is, next to the well-known positive and negative symptoms, characterized by a cognitive and motor deterioration. Although there still is conflicting evidence whether this deterioration has a neurodegenerative etiology, it has been suggested that some motor and cognitive changes in schizophrenia resemble those observed during normal ageing[51,52]. In contrast to extensively demonstrated deficits in explicit learning, it remains unclear whether implicit learning is impaired in schizophrenia and normal ageing. We performed a non-interventional study, using a wide battery of motor and cognitive tests, in order to observe which motor and cognitive processes are most disrupted in schizophrenia and to test whether patients with schizophrenia would show similar patterns of cognitive and motor deficits as elderly participants.

In this thesis, 30 stable schizophrenia patients were compared with 30 healthy age- and sex-matched controls and 30 elderly controls (>65 years) on six categories of motor learning: motor speed, writing, tracking, single aiming, as well as explicit and implicit adaptation and explicit and implicit sequence learning. The tasks, which were performed on 2 consecutive days and after one week, are described in detail in Chapter II and their analyses and results are depicted in the subsequent Chapters.

All patients and elderly individuals showed significant learning across all tasks but even on the simplest motor tasks patients with schizophrenia showed considerable motor slowing. Our investigation revealed distinct patterns of reduced motor abilities between the two experimental groups. Specifically, the elderly performed worse on tasks requiring more complexity and fine motor control, such as tracking, writing numbers in the SDST and explicit sequence learning, probably due to a less accurate and more variable motor output system. Individuals with schizophrenia performed worse on implicit and explicit adaptation and on most of tests that require more explicit, cognitive capacities, including verbal learning. This suggests different neurobiological underpinnings between ageing and schizophrenia which challenges the notion of the accelerated ageing

hypothesis of schizophrenia. The severity of positive symptoms in schizophrenia seemed to be associated with adaptation deficits.

This thesis supports the notion that many specific subprocesses contribute to psychomotor slowing in schizophrenia, and that the relationship between cognitive and motor subprocesses is strongly intertwined. Considering the well-established neural foundations of sequence learning and adaptation paradigms, these were chosen as the primary domains of investigation. To capture the cognitive contributions to learning, we utilized methods to extract the explicit cognitive engagement within these domains. Our findings highlight that an explicit learning component holds significant sway within sequence and adaptation tasks, domains that have historically been perceived as primarily implicit. This underscores the need for a comprehensive reevaluation of the role of explicit cognitive processes in motor skill acquisition paradigms. Future research is urged to devise methodologies for capturing these cognitive mechanisms in rudimentary motor tasks. With a more elaborate comprehension of psychomotor slowing's underpinnings, we might pave the way for more targeted pharmaceutical interventions and refined rehabilitation strategies.

This thesis conveys an optimistic message: considering the relatively well-preserved motor learning abilities, these aspects could be addressed in the development of rehabilitation programs and pharmacological treatments in order to improve everyday cognitive and motor functioning in patients with schizophrenia.

CHAPTER X – SAMENVATTING

Schizofrenie is een ernstige stoornis die, naast de gekende positieve en negatieve symptomen, wordt gekenmerkt door een cognitieve en motorische achteruitgang. Hoewel er nog steeds tegenstrijdig bewijs is of deze achteruitgang een neurodegeneratieve oorzaak heeft, wordt gesuggereerd dat sommige motorische en cognitieve veranderingen bij schizofrenie lijken op diegene die waargenomen worden bij normale veroudering[51,106]. In tegenstelling tot de uitgebreid gedocumenteerde tekorten op vlak van expliciet leren, blijft het onduidelijk of impliciet leren is aangetast bij schizofrenie en normale veroudering. We hebben een niet-interventionele studie uitgevoerd met een brede reeks motorische en cognitieve taken om te observeren welke motorische en cognitieve processen het meest verstoord zijn bij schizofrenie en om te testen of patiënten met schizofrenie vergelijkbare cognitieve en motorische tekorten vertonen als oudere deelnemers.

In deze thesis werden 30 stabiele patiënten met schizofrenie vergeleken met 30 gezonde, leeftijd- en geslachtsgematchte controles en 30 oudere controles (ouder dan 65 jaar) op zes categorieën van motorisch leren: motorische snelheid, schrijven, volgtaken, evenals expliciet en impliciet adaptatie en sequentieel leren. Deze taken, die gedurende 2 opeenvolgende dagen en na één week werden uitgevoerd, worden gedetailleerd beschreven in Hoofdstuk II en de analyses en resultaten per taak in de daaropvolgende hoofdstukken.

Alle patiënten en oudere personen vertoonden een significant leervermogen op alle taken, maar zelfs bij de eenvoudigste taken vertoonden patiënten met schizofrenie een aanzienlijke motorische vertraging. Deze thesis onthulde verschillende patronen van motorische tekorten tussen de twee experimentele groepen. Zo presteerden ouderen slechter op taken die complexer waren en meer fijne motorische controle vereisen, zoals volgtaken, het schrijven van getallen in de SDST en expliciet sequentieel leren. Dit is waarschijnlijk het gevolg van een minder nauwkeurig en variabeler motorisch uitvoeringssysteem. Personen met schizofrenie presteerden slechter op adaptatietaken en op taken die meer expliciet-cognitieve capaciteiten vereisen, waaronder verbaal leren. Dit

suggereert dat er een verschillende neurobiologische basis is bij veroudering en schizofrenie, wat de neurodegeneratiehypothese van schizofrenie in twijfel trekt. Het hebben van meer positieve symptomen bij schizofrenie leek geassocieerd te zijn met meer problemen op vlak van adaptatievermogen.

Deze thesis ondersteunt het idee dat er veel verschillende subprocessen bijdragen aan psychomotorische vertraging, en dat de cognitieve en motorische subprocessen sterk met elkaar verweven zijn. Omdat de neurobiologische achtergrond van sequentieleren en adaptatie reeds goed gekend waren, werden deze twee paradigmata gekozen als de primaire onderzoeksgebieden van dit proefschrift. We gebruikten specifieke methodes om de cognitieve van de motorische componenten binnen de verschillende leertaken te scheiden. Onze bevindingen benadrukken echter dat het zeer moeilijk is om deze expliciete (cognitieve) componenten uit de impliciete taken weg te filteren en vice versa. Deze cognitieve processen blijken zelfs een aanzienlijke rol binnen sequentie- en adaptatieleren te spelen, hetgeen motorische paradigma's zijn die tot voor kort voornamelijk als impliciet werden beschouwd. Dit onderstreept de noodzaak van een heroverweging van de rol van expliciete processen in motorische leerparadigma's. We hopen dat in toekomstig onderzoek methodologieën ontwikkeld worden om de verschillende submechanismen nog nauwkeuriger te kunnen vastleggen.

Deze thesis brengt een optimistische boodschap over: motorisch leervermogen blijft relatief gespaard bij schizofrenie, hetgeen kan worden aangewend in revalidatieprogramma's en van belang is bij de ontwikkeling van farmacologische producten die gericht zijn op de verbetering van de cognitieve en motorische functies bij schizofrenie.

REFERENCES

1. Rössler W, Salize HJ, van Os J, Riecher-Rössler A. Size of burden of schizophrenia and psychotic disorders. *Eur Neuropsychopharmacol*. 2005;15(4):399-409. doi:10.1016/j.euroneuro.2005.04.009

2. Tandon R. Putting the cart before the horse. Schizophrenia does need a name change, but the time is not right. *Schizophr Res*. 2022;240:22-23. doi:10.1016/j.schres.2021.11.050

3. Green MF, Nuechterlein KH, Gold JM, et al. Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICS conference to select cognitive domains and test criteria. *Biol Psychiatry*. 2004;56(5):301-307. doi:10.1016/j.biopsych.2004.06.023

4. Morrens M, Walther S. *Psychomotor Symptomatology in Psychiatric Illnesses*.; 2015. doi:10.3389/978-2-88919-725-5

5. Abboud R, Noronha C, Diwadkar VA. Motor system dysfunction in the schizophrenia diathesis: Neural systems to neurotransmitters. *European Psychiatry*. 2017;44:125-133. doi:10.1016/j.eurpsy.2017.04.004

6. Lisi G, Nico D, Ribolsi M, et al. Asymmetries in initiation of aiming movements in schizophrenia. *Neuropsychologia*. 2018;109(December 2017):200-207. doi:10.1016/j.neuropsychologia.2017.12.030

7. Morrens M, Hulstijn W, Sabbe B. Psychomotor slowing in schizophrenia. *Schizophr Bull*. 2007;33(4):1038-1053. doi:10.1093/schbul/sbl051

8. Docx L, Sabbe B, Fransen E, et al. Longitudinal evaluation of the psychomotor syndrome in schizophrenia. *Journal of Neuropsychiatry and Clinical Neurosciences*. 2014;26(4):359-368. doi:10.1176/appi.neuropsych.13020027/asset/images/large/appi.neuropsych.13020027f1.jpeg

9. Peralta V, de Jalón EG, Campos MS, Cuesta MJ. Covariation between motor signs and negative symptoms in drug-naive subjects with schizophrenia-spectrum disorders before and after antipsychotic

treatment. *Schizophr Res*. Published online 2017. doi:10.1016/j.schres.2017.08.039

10. Morrens M, Hulstijn W, Sabbe B. The effects of atypical and conventional antipsychotics on reduced processing speed and psychomotor slowing in schizophrenia: A cross-sectional exploratory study. *Clin Ther*. 2008;30(4):684-692. doi:10.1016/j.clinthera.2008.04.012

11. Morrens M, Hulstijn W, Sabbe B. Psychomotor slowing in schizophrenia. *Schizophr Bull*. 2007;33(4):1038-1053. doi:10.1093/schbul/sbl051

12. Hirjak D, Meyer-Lindenberg A, Kubera KM, Thomann PA, Wolf RC. Motor dysfunction as research domain in the period preceding manifest schizophrenia: A systematic review. *Neurosci Biobehav Rev*. 2018;87:87-105. doi:10.1016/j.neubiorev.2018.01.011

13. Wolpert DM, Diedrichsen J, Flanagan JR, et al. Gesture impairments in schizophrenia are linked to increased movement and prolonged motor planning and execution. *Schizophr Res*. 2014;33(4):535-544. doi:10.1038/nrn3112

14. Cuesta MJ, Peralta V. Modeling neuromotor pathology in schizophrenia : A window to brain mechanisms and clinical insight into the syndrome. *Schizophr Res*. 2018;200:1-4. doi:10.1016/j.schres.2018.05.040

15. Osborne KJ, Walther S, Shankman SA, Mittal VA. Psychomotor slowing in Schizophrenia: Implications for endophenotype and biomarker development. *Biomark Neuropsychiatry*. 2020;2(February):100016. doi:10.1016/j.bionps.2020.100016

16. Hirjak D, Meyer-Lindenberg A, Sambataro F, Christian Wolf R. Sensorimotor Neuroscience in Mental Disorders: Progress, Perspectives and Challenges. *Schizophr Bull*. 2021;47(4):880-882. doi:10.1093/schbul/sbab053

17. Nadesalingam N, Chapellier V, Lefebvre S, et al. Motor abnormalities are associated with poor social and functional outcomes in

schizophrenia. *Compr Psychiatry*. 2022;115. doi:10.1016/j.comppsych.2022.152307

18. Deister A, Marneros A. Prognostic value of initial subtype in schizophrenic disorders. *Schizophr Res*. 1994;12(2):145-157. Accessed October 1, 2014. http://www.ncbi.nlm.nih.gov/pubmed/8043525

19. Fiszdon JM, McClough JF, Silverstein SM, Bell MD, Jaramillo JR, Smith TE. Learning potential as a predictor of readiness for psychosocial rehabilitation in schizophrenia. *Psychiatry Res*. 2006;143(2-3):159-166. doi:10.1016/j.psychres.2005.09.012

20. Morrens M, Hulstijn W, Matton C, et al. Delineating psychomotor slowing from reduced processing speed in schizophrenia. *Cogn Neuropsychiatry*. 2008;13(6):457-471. doi:10.1080/13546800802439312

21. Krakauer JW, Hadjiosif AM, Xu J, Wong AL, Haith AM. Motor learning. *Compr Physiol*. 2019;9(2):613-663. doi:10.1002/cphy.c170043

22. Houthoofd S, Morrens M, Hulstijn W, Sabbe B. Differentiation between deviant trajectory planning, action planning, and reduced psychomotor speed in schizophrenia. *Cogn Neuropsychiatry*. 2013;18(4):284-303. doi:10.1080/13546805.2012.708654

23. Janssens S, Moens H, Coppens V, et al. Psychomotor assessment as a tool to differentiate schizophrenia from other psychotic disorders. *Schizophr Res*. 2016;(2016). doi:10.1016/j.schres.2017.06.047

24. Hirjak D, Meyer-Lindenberg A, Kubera KM, Thomann PA, Wolf RC. Motor dysfunction as research domain in the period preceding manifest schizophrenia: A systematic review. *Neurosci Biobehav Rev*. 2018;87:87-105. doi:10.1016/J.NEUBIOREV.2018.01.011

25. Bernard JA, Mittal VA. Dysfunctional Activation of the Cerebellum in Schizophrenia: A Functional Neuroimaging Meta-Analysis. *Clin Psychol Sci*. 2015;3(4):545-566. doi:10.1177/2167702614542463

26. Mittal VA, Bernard JA, Northoff G. What Can Different Motor Circuits Tell Us About Psychosis? An RDoC Perspective. *Schizophr Bull*. 2017;43(5):949-955. doi:10.1093/schbul/sbx087

27. Mittal VA, Bernard JA, Walther S. Cerebellar-thalamic circuits play a critical role in psychomotor function. *Mol Psychiatry*. Published online 2020. doi:10.1038/s41380-020-00935-9

28. Northoff G, Hirjak D, Wolf RC, Magioncalda P, Martino M. All roads lead to the motor cortex: psychomotor mechanisms and their biochemical modulation in psychiatric disorders. *Molecular Psychiatry 2020 26:1*. 2020;26(1):92-102. doi:10.1038/s41380-020-0814-5

29. Mittal VA, Bernard JA, Walther S. Cerebellar-thalamic circuits play a critical role in psychomotor function. *Molecular Psychiatry 2020 26:8*. 2020;26(8):3666-3668. doi:10.1038/s41380-020-00935-9

30. Northoff G, Hirjak D, Wolf RC, Magioncalda P, Martino M. All roads lead to the motor cortex: psychomotor mechanisms and their biochemical modulation in psychiatric disorders. *Mol Psychiatry*. 2021;26(1):92-102. doi:10.1038/S41380-020-0814-5

31. Nuechterlein KH, Green MF, Kern RS, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *Am J Psychiatry*. 2008;165(2):203-213. doi:10.1176/appi.ajp.2007.07010042

32. Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. *Schizophr Res*. 2004;72(1):29-39. doi:10.1016/j.schres.2004.09.007

33. Juston Osborne K, Walther S, Shankman SA, Mittal VA. Psychomotor slowing in Schizophrenia: Implications for endophenotype and biomarker development. Published online 2020. doi:10.1016/j.bionps.2020.100016

34. Schäppi L, Stegmayer K, Viher P V, Walther S. Distinct associations of Motor Domains in relatives of schizophrenia Patients — Different Pathways to Motor abnormalities in schizophrenia ? *Front Psychiatry*. 2018;9(April):1-12. doi:10.3389/fpsyt.2018.00129

35. Hirjak D, Meyer-Lindenberg A, Kubera KM, Thomann PA, Wolf RC. Motor dysfunction as research domain in the period preceding

manifest schizophrenia: A systematic review. *Neurosci Biobehav Rev*. 2018;87:87-105. doi:10.1016/j.neubiorev.2018.01.011

36. Pascual-Leone A, Grafman J, Clark K, et al. Procedural learning in Parkinson's disease and cerebellar degeneration. *Ann Neurol*. 1993;34(4):594-602. doi:10.1002/ANA.410340414

37. Krakauer JW, Hadjiosif AM, Xu J, Wong AL, Haith AM. Motor Learning. *Compr Physiol*. 2019;9(2):613-663. doi:10.1002/CPHY.C170043

38. Stark-Inbar A, Raza M, Taylor JA, Ivry RB. Individual differences in implicit motor learning: task specificity in sensorimotor adaptation and sequence learning. *J Neurophysiol*. 2017;117(1):412-428. doi:10.1152/jn.01141.2015

39. Ranganathan R, Tomlinson AD, Lokesh R, Lin TH, Patel P. A tale of too many tasks: task fragmentation in motor learning and a call for model task paradigms. *Exp Brain Res*. 2021;239(1):1-19. doi:10.1007/s00221-020-05908-6

40. Taylor JA, Krakauer JW, Ivry RB. Explicit and Implicit Contributions to Learning in a Sensorimotor Adaptation Task. *Journal of Neuroscience*. 2014;34(8):3023-3032. doi:10.1523/JNEUROSCI.3619-13.2014

41. Hadjiosif AM, Krakauer JW. The explicit/implicit distinction in studies of visuomotor learning: Conceptual and methodological pitfalls. *European Journal of Neuroscience*. 2021;53(2):499-503. doi:10.1111/EJN.14984

42. Shadmehr R, Krakauer JW. A computational neuroanatomy for motor control. *Exp Brain Res*. 2008;185(3):359-381. doi:10.1007/s00221-008-1280-5

43. Remillard G. The study of sequence learning in individuals with schizophrenia: A critical review of the literature. *J Neuropsychol*. Published online 2013:231-245. doi:10.1111/jnp.12022

44. Horan WP, Green MF, Knowlton BJ, Wynn JK, Mintz J, Nuechterlein KH. Impaired implicit learning in schizophrenia. *Neuropsychology*. 2008;22(5):606-617. doi:10.1037/a0012602

45. Pedersen A, Siegmund A, Ohrmann P, et al. Reduced implicit and explicit sequence learning in first-episode schizophrenia. *Neuropsychologia*. 2008;46(1):186-195. doi:10.1016/j.neuropsychologia.2007.07.021

46. Siegert RJ, Weatherall M, Bell EM. Is implicit sequence learning impaired in schizophrenia? A meta-analysis. *Brain Cogn*. 2008;67(3):351-359. doi:10.1016/j.bandc.2008.02.005

47. Gomar JJ, Pomarol-Clotet E, Sarró S, Salvador R, Myers CE, McKenna PJ. Procedural learning in schizophrenia: reconciling the discrepant findings. *Biol Psychiatry*. 2011;69(1):49-54. doi:10.1016/j.biopsych.2010.07.013

48. Purdon SE, Waldie B, Woodward ND, Wilman AH, Tibbo PG. Procedural learning in first episode schizophrenia investigated with functional magnetic resonance imaging. *Neuropsychology*. 2011;25(2):147-158.

49. Seidler RD, Carson RG. Sensorimotor Learning: Neurocognitive Mechanisms and Individual Differences. *J Neuroeng Rehabil*. 2017;14(1):1-7. doi:10.1186/s12984-017-0279-1

50. Seidler RD, Carson RG. Sensorimotor Learning: Neurocognitive Mechanisms and Individual Differences. *J Neuroeng Rehabil*. 2017;14(1). doi:10.1186/S12984-017-0279-1

51. Kirkpatrick B, Kennedy BK. Accelerated aging in schizophrenia and related disorders: Future research. *Schizophr Res*. 2018;196:4-8. doi:10.1016/j.schres.2017.06.034

52. Kirkpatrick B, Messias E, Harvey PD, Fernandez-Egea E, Bowie CR. Is schizophrenia a syndrome of accelerated aging? *Schizophr Bull*. 2008;34(6):1024-1032. doi:10.1093/schbul/sbm140

53. Semmler JG, Hand BJ, Sasaki R, Merkin A, Opie GM. Age-related changes in motor cortex plasticity assessed with non-invasive brain stimulation: an update and new perspectives. *Exp Brain Res*. 2021;239(9):2661-2678. doi:10.1007/s00221-021-06163-z

54. Cirillo J. Physical activity, motor performance and skill learning: a focus on primary motor cortex in healthy aging. *Exp Brain Res*. 2021;239(12):3431-3438. doi:10.1007/s00221-021-06218-1

55. Hooyman A, Wang P, Schaefer SY. Age-related differences in functional tool-use are due to changes in movement quality and not simply motor slowing. *Exp Brain Res*. 2021;239(5):1617-1626. doi:10.1007/s00221-021-06084-x

56. Voelcker-Rehage C. Motor-skill learning in older adults-a review of studies on age-related differences. *European Review of Aging and Physical Activity*. 2008;5(1):5-16. doi:10.1007/s11556-008-0030-9

57. King BR, Fogel SM, Albouy G, Doyon J. Neural correlates of the age-related changes in motor sequence learning and motor adaptation in older adults. *Front Hum Neurosci*. 2013;7(April):1-13. doi:10.3389/fnhum.2013.00142

58. Heuer H, Hegele M. Generalization of implicit and explicit adjustments to visuomotor rotations across the workspace in younger and older adults. *J Neurophysiol*. 2011;106(4):2078-2085. doi:10.1152/jn.00043.2011

59. Lei Y, Wang J. The effect of proprioceptive acuity variability on motor adaptation in older adults. *Exp Brain Res*. 2018;236(2):599-608. doi:10.1007/s00221-017-5150-x

60. Bootsma JM, Caljouw SR, Veldman MP, Maurits NM, Rothwell JC, Hortobágyi T. Neural Correlates of Motor Skill Learning Are Dependent on Both Age and Task Difficulty. *Front Aging Neurosci*. 2021;13. doi:10.3389/fnagi.2021.643132

61. De Picker LJ, Cornelis C, Hulstijn W, et al. Stable schizophrenia patients learn equally well as age-matched controls and better than elderly controls in two sensorimotor rotary pursuit tasks. *Front Psychiatry*. 2014;5:165. doi:10.3389/fpsyt.2014.00165

62. Hulstijn W, Cornelis C, Morsel A, Timmers M, Morrens · Manuel, Sabbe BGC. Motor learning and performance in schizophrenia and aging: two

different patterns of decline. *Exp Brain Res*. 2024;242:879-899. doi:10.1007/s00221-024-06797-9

63. Cornelis C, De Picker LJ, Hulstijn W, et al. Preserved learning during the Symbol Digit Substitution Test in patients with schizophrenia, age-matched controls and elderly. *Front Psychiatry*. 2014;5. doi:10.3389/fpsyt.2014.00189

64. Cornelis C, De Picker LJ, De Boer P, et al. Implicit motor sequence learning in schizophrenia and in old age: reduced performance only in the third session. *Exp Brain Res*. 2016;234(12):3531-3542. doi:10.1007/s00221-016-4751-0

65. Cornelis C, De Picker LJ, Coppens V, et al. Impaired Sensorimotor Adaption in Schizophrenia in Comparison to Age-Matched and Elderly Controls. *Neuropsychobiology*. Published online 2021:1-14. doi:10.1159/000518867

66. The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations - PubMed. Accessed August 15, 2023. https://pubmed.ncbi.nlm.nih.gov/2695141/

67. Andreasen NC. Scale for the assessment of positive symptoms (SAPS). Published online 2000. Accessed August 15, 2023. https://iro.uiowa.edu/esploro/outputs/other/Scale-for-the-assessment-of-positive/9984097080502771

68. L. De Picker, C. Cornelis, W. Hulstijn, G. Dumont, E. Fransen, M. Morrens BS. Preserved sensorimotor learning in stable schizophrenia patients but not in elderly participants compared to young controls in two variations of the Rotary Pursuit. *Front Psychiatry*.

69. Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophr Res*. 2004;72(1):41-51. doi:10.1016/J.SCHRES.2004.09.009

70. Squire LR. Declarative and Nondeclarative Memory: Multiple Brain Systems Supporting Learning and Memory. *J Cogn Neurosci*. 1992;4(3):232-243. doi:10.1162/JOCN.1992.4.3.232

71. Marsh R, Alexander GM, Packard MG, Zhu H, Peterson BS. Perceptual-motor skill learning in Gilles de la Tourette syndrome: Evidence for multiple procedural learning and memory systems. *Neuropsychologia*. 2005;43(10):1456-1465. doi:10.1016/J.NEUROPSYCHOLOGIA.2004.12.012

72. Ammons RB. Acquisition of motor skill: II. Rotary pursuit performance with continuous practice before and after a single rest. *J Exp Psychol*. 1947;37(5):393-411. doi:10.1037/H0054334

73. Roth RM, Baribeau J, Milovan D, O'Connor K, Todorov C. Procedural and declarative memory in obsessive-compulsive disorder. *Journal of the International Neuropsychological Society*. 2004;10(5):647-654. doi:10.1017/S1355617704105018

74. Graybiel AM, Aosaki T, Flaherty AW, Kimura M. The Basal Ganglia and Adaptive Motor Control. *Science (1979)*. 1994;265(5180):1826-1831. doi:10.1126/SCIENCE.8091209

75. Doyon J, Bellec P, Amsel R, et al. Contributions of the basal ganglia and functionally related brain structures to motor learning. *Behavioural Brain Research*. 2009;199(1):61-75. doi:10.1016/J.BBR.2008.11.012

76. Huston PE, Shakow D. Learning capacity in schizophrenia. *https://doi.org/101176/ajp10512881*. 2006;105(12):881-888. doi:10.1176/AJP.105.12.881

77. Torrey EF, Goto TM, Ragland JD, Bigelow LB, Weinberger DR. Learning and memory in monozygotic twins discordant for schizophrenia. *Psychol Med*. 1993;23(1):71-85. doi:10.1017/S0033291700038861

78. Granholm E, Bartzokis G, Asarnow RF, Marder SR. Preliminary associations between motor procedural learning, basal ganglia T2 relaxation times, and tardive dyskinesia in schizophrenia. *Psychiatry Res Neuroimaging*. 1993;50(1):33-44. doi:10.1016/0925-4927(93)90022-A

79. Clare L, McKenna PJ, Mortimer AM, Baddeley AD. Memory in schizophrenia: What is impaired and what is preserved?

Neuropsychologia. 1993;31(11):1225-1241. doi:10.1016/0028-3932(93)90070-G

80. Schwartz BL, Rosse RB, Veazey C, Deutsch SI. Impaired motor skill learning in schizophrenia: Implications for corticostriatal dysfunction. *Biol Psychiatry*. 1996;39(4):241-248. doi:10.1016/0006-3223(95)00130-1

81. Kern RS, Green MF, Wallace CJ. Declarative and Procedural Learning in Schizophrenia: A Test of the Integrity of Divergent Memory Systems. *http://dx.doi.org/101080/135468097396405*. 2010;2(1):39-50. doi:10.1080/135468097396405

82. Weickert TW, Terrazas A, Bigelow LB, et al. Habit and Skill Learning in Schizophrenia: Evidence of Normal Striatal Processing With Abnormal Cortical Input. *Learning & Memory*. 2002;9(6):430-442. doi:10.1101/LM.49102

83. Gold JM, Hahn B, Strauss GP, Waltz JA. Turning it upside down: Areas of preserved cognitive function in schizophrenia. *Neuropsychol Rev*. 2009;19(3):294-311. doi:10.1007/S11065-009-9098-X/METRICS

84. Weickert TW, Terrazas A, Bigelow LB, et al. Habit and Skill Learning in Schizophrenia : Evidence of Normal Striatal Processing With Abnormal Cortical Input. doi:10.1101/lm.49102.Only

85. Kennedy KM, Partridge T, Raz N. Age-Related Differences in Acquisition of Perceptual-Motor Skills: Working Memory as a Mediator. *http://dx.doi.org/101080/13825580601186650*. 2008;15(2):165-183. doi:10.1080/13825580601186650

86. Siegel D. A Multivariate Study of Pursuit Rotor Skill Development. *http://dx.doi.org/101080/02701367199010608676*. 2013;61(2):201-205. doi:10.1080/02701367.1990.10608676

87. Gomar JJ, Pomarol-Clotet E, Sarr S, Salvador R, Myers CE, McKenna PJ. Procedural learning in schizophrenia: Reconciling the discrepant findings. *Biol Psychiatry*. 2011;69(1):49-54. doi:10.1016/j.biopsych.2010.07.013

88. Van Erp TGM, Preda A, Nguyen D, et al. Converting positive and negative symptom scores between PANSS and SAPS/SANS. *Schizophr Res*. 2014;152(1):289-294. doi:10.1016/J.SCHRES.2013.11.013

89. Weickert TW, Goldberg TE, Gold JM, Bigelow LB, Egan MF, Weinberger DR. Cognitive Impairments in Patients With Schizophrenia Displaying Preserved and Compromised Intellect. *Arch Gen Psychiatry*. 2000;57(9):907-913. doi:10.1001/ARCHPSYC.57.9.907

90. Salazar-Fraile J, Balanzá-Martínez V, Selva-Vera G, et al. Motor speed predicts stability of cognitive deficits in both schizophrenic and bipolar I patients at one-year follow-up. *Eur J Psychiatry*. 2009;23(3):184-197. Accessed August 15, 2023. https://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S0213-61632009000300007&lng=en&nrm=iso&tlng=en

91. Cuesta MJ, Sánchez-Torres AM, De Jalón EG, et al. Spontaneous Parkinsonism Is Associated With Cognitive Impairment in Antipsychotic-Naive Patients With First-Episode Psychosis: A 6-Month Follow-up Study. *Schizophr Bull*. 2014;40(5):1164-1173. doi:10.1093/SCHBUL/SBT125

92. Morrens M, Hulstijn W, Sabbe B. The effects of atypical and conventional antipsychotics on reduced processing speed and psychomotor slowing in schizophrenia: A cross-sectional exploratory study. *Clin Ther*. 2008;30(4):684-692. doi:10.1016/j.clinthera.2008.04.012

93. Ghisletta P, Kennedy KM, Rodrigue KM, Lindenberger U, Raz N. Adult Age Differences and the Role of Cognitive Resources in Perceptual–Motor Skill Acquisition: Application of a Multilevel Negative Exponential Model. *The Journals of Gerontology: Series B*. 2010;65B(2):163-173. doi:10.1093/GERONB/GBP126

94. Weinberger DR, Gallhofer B. Cognitive function in schizophrenia. *Int Clin Psychopharmacol*. 1997;12 Suppl 4:S29-36. Accessed August 20, 2014. http://www.ncbi.nlm.nih.gov/pubmed/9352344

95. Nuechterlein KH, Ventura J, Subotnik KL, Bartzokis G. The early longitudinal course of cognitive deficits in schizophrenia. *J Clin Psychiatry*. 2014;75 Suppl 2:25-29. doi:10.4088/JCP.13065.su1.06

96. Brébion G, Amador X, Smith MJ, Gorman JM. Memory impairment and schizophrenia: the role of processing speed. *Schizophr Res*. 1998;30(1):31-39. http://www.ncbi.nlm.nih.gov/pubmed/9542786

97. Pashler H. Dual-task interference in simple tasks: data and theory. *Psychol Bull*. 1994;116(2):220-244. Accessed September 26, 2014. http://www.ncbi.nlm.nih.gov/pubmed/7972591

98. Dickinson D, Ramsey ME, Gold JM. Overlooking the Obvious. 2007;64(May).

99. Knowles EEM, David AS, Reichenberg A. Processing speed deficits in schizophrenia: reexamining the evidence. *Am J Psychiatry*. 2010;167(7):828-835. doi:10.1176/appi.ajp.2010.09070937

100. Morrens M, Hulstijn W, Van Hecke J, Peuskens J, Sabbe BGC. Sensorimotor and cognitive slowing in schizophrenia as measured by the Symbol Digit Substitution Test. *J Psychiatr Res*. 2006;40(3):200-206. doi:10.1016/j.jpsychires.2005.04.014

101. Horan WP, Green MF, Knowlton BJ, Wynn JK. Impaired Implicit Learning in Schizophrenia. 2009;22(5):606-617. doi:10.1037/a0012602.Impaired

102. McDowd J, Tang TC, Tsai PC, Wang SY, Su CY. The association between verbal memory, processing speed, negative symptoms and functional capacity in schizophrenia. *Psychiatry Res*. 2011;187(3):329-334. doi:10.1016/j.psychres.2011.01.017

103. Bachman P, Reichenberg A, Rice P, et al. Deconstructing processing speed deficits in schizophrenia: application of a parametric digit symbol coding test. *Schizophr Res*. 2010;118(1-3):6-11. doi:10.1016/j.schres.2010.02.1029

104. Joy S, Fein D, Kaplan E. Decoding digit symbol: speed, memory, and visual scanning. *Assessment*. 2003;10(1):56-65. Accessed August 20, 2014. http://www.ncbi.nlm.nih.gov/pubmed/12675384

105. Lezak, M.D., Howieson, D.B., & Loring DW. *Neuropsychological Assessment.*; 2004.

106. Kirkpatrick B, Messias E, Harvey PD, Fernandez-Egea E, Bowie CR. Is schizophrenia a syndrome of accelerated aging? *Schizophr Bull*. 2007;34(6):1024-1032. doi:10.1093/schbul/sbm140

107. John R. Crawford, Janet Bryan MAL. The Executive Decline Hypothesis of Cognitive Aging: Do Executive Deficits Qualify as Differential Deficits and Do They Mediate Age-Related Memory Decline?*. Aging, Neuropsychology, and Cognition. Published 2000. Accessed August 27, 2014. http://homepages.abdn.ac.uk/j.crawford/pages/dept/pdfs/Aging_Neuro_Cog_2000_frontalhyp.pdf

108. Baudouin A, Clarys D, Vanneste S, Isingrini M. Executive functioning and processing speed in age-related differences in memory: contribution of a coding task. *Brain Cogn*. 2009;71(3):240-245. doi:10.1016/j.bandc.2009.08.007

109. Salthouse TA. The role of memory in the age decline in digit-symbol substitution performance. *J Gerontol*. 1978;33(2):232-238. Accessed September 15, 2014. http://www.ncbi.nlm.nih.gov/pubmed/637915

110. Mahurin RK, Velligan DI, Miller AL. Executive-frontal lobe cognitive dysfunction in schizophrenia: A symptom subtype analysis. *Psychiatry Res*. 1998;79(2):139-149. doi:10.1016/S0165-1781(98)00031-6

111. Woodward ND, Duffy B, Karbasforoushan H. Prefrontal cortex activity during response selection predicts processing speed impairment in schizophrenia. *J Int Neuropsychol Soc*. 2013;19(7):782-791. doi:10.1017/S1355617713000532

112. Krieger S, Lis S, Janik H, Cetin T, Gallhofer B, Meyer-Lindenberg A. Executive function and cognitive subprocesses in first-episode, drug-naive schizophrenia: an analysis of N-back performance. *Am J Psychiatry*. 2005;162(6):1206-1208. doi:10.1176/appi.ajp.162.6.1206

113. van Erp TGM, Preda A, Nguyen D, et al. Converting positive and negative symptom scores between PANSS and SAPS/SANS. *Schizophr Res*. 2014;152(1):289-294. doi:10.1016/j.schres.2013.11.013

114. Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. doi:10.1016/j.schres.2004.09.009

115. Bin Tang, Wei-li Chan, Caroline M. Lanigan, Brian Dean, J. Gregor Sutcliffe EAT. Normal Human Aging and Early-Stage Schizophrenia Share Common Molecular Profiles. *Aging Cell*. 2009;8(3):339-342. doi:10.1016/j.surg.2006.10.010.Use

116. Heaton R, Paulsen JS, McAdams LA, et al. Neuropsychological deficits in schizophrenics. Relationship to age, chronicity, and dementia. *Arch Gen Psychiatry*. 1994;51(6):469-476. Accessed April 14, 2016. https://www.researchgate.net/publication/15005815_Heaton_RK_Paulsen_JS_McAdams_LA_Kuck_J_Zisook_S_Braff_D_et_al_Neuropsychological_deficits_in_schizophrenics_Relationship_to_age_chronicity_and_dementia_Arch_Gen_Psychiatry_51_469-476

117. Bowie CR, Harvey PD. Treatment of cognitive deficits in schizophrenia. *Current Opinion in Investigational Drugs*. 2006;7(7). Accessed April 14, 2016. https://miami.pure.elsevier.com/en/publications/treatment-of-cognitive-deficits-in-schizophrenia

118. Kalkstein S, Hurford I, Gur RC. Neurocognition in schizophrenia. *Curr Top Behav Neurosci*. 2010;4:373-390. Accessed December 8, 2015. http://www.ncbi.nlm.nih.gov/pubmed/21312407

119. Howard, Jr JH, Howard D V. Aging mind and brain : is implicit learning spared in healthy aging ? 2013;4(November):1-6. doi:10.3389/fpsyg.2013.00817

120. Verneau M, van der Kamp J, Savelsbergh GJP, de Looze MP. Age and Time Effects on Implicit and Explicit Learning. *Exp Aging Res*. 2014;40(4):477-511. doi:10.1080/0361073X.2014.926778

121. Seger CA. Implicit learning. *Psychol Bull*. 1994;115(2):163-196. doi:http://psycnet.apa.org/doi/10.1037/0033-2909.115.2.163

122. D Baddeley A. *The Handbook of Memory Disorders*.; 2002. doi:10.1016/S0165-0114(83)80081-5

123. Ashe J, Lungu O V., Basford AT, Lu X. Cortical control of motor sequences. *Curr Opin Neurobiol*. 2006;16(2):213-221. doi:10.1016/J.CONB.2006.03.008

124. King BR, Fogel SM, Albouy G, Doyon J. Neural correlates of the age-related changes in motor sequence learning and motor adaptation in older adults. *Front Hum Neurosci*. 2013;7(April):1-13. doi:10.3389/fnhum.2013.00142

125. Marvel CL, Schwartz BL, Howard D V, Howard, Jr JH. Implicit learning of non-spatial sequences in schizophrenia. *J Int Neuropsychol Soc*. 2005;11(6):659-667.

126. Nissen, M.J. and Bullemer P. Attentional requirement of learning: Evidence from performance measures. *Cognit Psychol*. 1987;19:1-32.

127. Hikosaka O, Sakai K, Lu X, et al. Parallel neural networks for learning sequential procedures. *Trends Neurosci*. 1999;22(10):464-471. doi:10.1016/S0166-2236(99)01439-3

128. Gold JM, Hahn B, Strauss GP, Waltz JA. Turning it upside down: Areas of preserved cognitive function in schizophrenia. *Neuropsychol Rev*. 2009;19(3):294-311. doi:10.1007/S11065-009-9098-X

129. Brown RM, Robertson EM, Press DZ. Sequence skill acquisition and off-line learning in normal aging. *PLoS One*. 2009;4(8):e6683. doi:10.1371/journal.pone.0006683

130. Adini Y, Bonneh YS, Komm S, Deutsch L, Israeli D. The time course and characteristics of procedural learning in schizophrenia patients and healthy individuals. *Front Hum Neurosci*. 2015;9(september):1-16. doi:10.3389/FNHUM.2015.00475/BIBTEX

131. Marvel C, Turner BM, O'Leary DS, et al. The Neural Correlates of Implicit Sequence Learning in Schizophrenia. *Neuropsychology*. 2007;21(6):761-777. doi:10.1037/0894-4105.21.6.761.

132. Janacsek K, Nemeth D. Implicit sequence learning and working memory: correlated or complicated? *Cortex*. 2013;49(8):2001-2006. doi:10.1016/j.cortex.2013.02.012

133. Hardoy MC, Carta MG, Catena M, et al. Impairment in visual and spatial perception in schizophrenia and delusional disorder. *Psychiatry Res*. 2004;127(1-2):163-166. doi:10.1016/J.PSYCHRES.2004.03.002

134. Khosravani N, Goodarzi MA. Patients with schizophrenia show deficits on spatial frequency doubling. *Vision Res*. 2013;93:49-53. doi:10.1016/J.VISRES.2013.10.007

135. Kravariti E, Toulopoulou T, Mapua-Filbey F, et al. Intellectual asymmetry and genetic liability in first-degree relatives of probands with schizophrenia. *Br J Psychiatry*. 2006;188(FEB.):186-187. doi:10.1192/BJP.BP.104.008177

136. Alescio-Lautier B, Michel BF, Herrera C, et al. Visual and visuospatial short-term memory in mild cognitive impairment and Alzheimer disease: Role of attention. *Neuropsychologia*. 2007;45(8):1948-1960. doi:10.1016/j.neuropsychologia.2006.04.033

137. Van Halteren-Van Tilborg I a D a, Scherder EJ a, Hulstijn W. Motor-Skill learning in Alzheimer's disease: A review with an eye to the clinical practice. *Neuropsychol Rev*. 2007;17(3):203-212. doi:10.1007/s11065-007-9030-1

138. Van Tilborg IA, Kessels RP, Kruijt P, Wester AJ, Hulstijn W. Spatial and nonspatial implicit motor learning in Korsakoff's amnesia: Evidence for selective deficits. *Exp Brain Res*. 2011;214(3):427-435. doi:10.1007/s00221-011-2841-6

139. Destrebecqz A, Peigneux P. Methods for studying unconscious learning. *Prog Brain Res*. 2005;150:69-80. doi:10.1016/S0079-6123(05)50006-2

140. Poldrack RA, Packard MG. Competition among multiple memory systems: Converging evidence from animal and human brain studies. *Neuropsychologia*. 2003;41(3):245-251. doi:10.1016/S0028-3932(02)00157-4

141. Mattay VS, Fera F, Tessitore A, et al. Neurophysiological correlates of age-related changes in human motor function. *Neurology*. 2002;58(4):630-635. Accessed January 3, 2016. http://www.ncbi.nlm.nih.gov/pubmed/11865144

142. Mushquash AR, Fawcett JM, Klein RM. Inhibition of return and schizophrenia: a meta-analysis. *Schizophr Res*. 2012;135(1-3):55-61. doi:10.1016/j.schres.2011.11.034

143. Smith CD, Walton A, Loveland AD, Umberger GH, Kryscio RJ, Gash DM. Memories that last in old age: motor skill learning and memory preservation. *Neurobiol Aging*. 2005;26(6):883-890. doi:10.1016/j.neurobiolaging.2004.08.014

144. Leucht S, Pitschel-Walz G, Abraham D, Kissling W. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. *Schizophr Res*. 1999;35(1):51-68. doi:10.1016/S0920-9964(98)00105-4

145. Oostwoud Wijdenes L, Brenner E, Smeets JBJ. Exposing sequence learning in a double-step task. *Exp Brain Res*. 2016;234(6):1701-1712. doi:10.1007/S00221-016-4566-Z/FIGURES/9

146. Perruchet, Pierre; Amorim MA. Conscious knowledge and changes in performance in sequence learning: Evidence against dissociation. *J Exp Psychol Learn Mem Cogn*. 1992;18(4):785-800.

147. Gaillard V, Cleeremans A, Destrebecqz A. Dissociating conscious and unconscious learning with objective and subjective measures. *Clin EEG Neurosci*. 2014;45(1):50-56. doi:10.1177/1550059413516757

148. Morrens M, Docx L, Walther S. Beyond boundaries: In search of an integrative view on motor symptoms in schizophrenia. *Front Psychiatry*. 2014;5(OCT):1-4. doi:10.3389/fpsyt.2014.00145

149. Walther S, Strik W. Motor symptoms and schizophrenia. *Neuropsychobiology*. 2012;66(2):77-92. doi:10.1159/000339456

150. Bernard J a, Seidler RD. Cerebellar contributions to visuomotor adaptation and motor sequence learning: an ALE meta-analysis. *Front Hum Neurosci*. 2013;7(February):27. doi:10.3389/fnhum.2013.00027

151. Block HJ, Bastian AJ. Cerebellar involvement in motor but not sensory adaptation. *Neuropsychologia*. 2012;50(8):1766-1775. doi:10.1016/j.neuropsychologia.2012.03.034

152. Garvey MA, Cuthbert BN. Developing a Motor Systems Domain for the NIMH RDoC Program. *Schizophr Bull*. 2017;43(5):935-936. doi:10.1093/schbul/sbx095

153. Izawa J, Asai T, Imamizu H. Computational motor control as a window to understanding schizophrenia. *Neurosci Res*. 2016;104:44-51. doi:10.1016/j.neures.2015.11.004

154. Diedrichsen J, Kornysheva K. Motor skill learning between selection and execution. *Trends Cogn Sci*. 2015;19(4):227-233. doi:10.1016/j.tics.2015.02.003

155. Bansal S, Murthy KG, Fitzgerald J, et al. Reduced transfer of visuomotor adaptation is associated with aberrant sense. Published online 2018.

156. Knoblich G, Stottmeister F, Kircher T. Self-monitoring in patients with schizophrenia. *Psychol Med*. 2004;34(8):1561-1569. doi:10.1017/S0033291704002454

157. McDougle SD, Ivry RB, Taylor JA. Taking Aim at the Cognitive Side of Learning in Sensorimotor Adaptation Tasks. *Trends Cogn Sci*. 2016;20(7):535-544. doi:10.1016/j.tics.2016.05.002

158. Bostan AC, Strick PL. The basal ganglia and the cerebellum: Nodes in an integrated network. *Nat Rev Neurosci*. 2018;19(6):338-350. doi:10.1038/s41583-018-0002-7

159. Wolpert DM, Diedrichsen J, Flanagan JR. Principles of sensorimotor learning. *Nat Rev Neurosci*. 2011;12(12). doi:10.1038/nrn3112

160. Criscimagna-Hemminger SE, Bastian AJ, Shadmehr R. Size of error affects cerebellar contributions to motor learning. *J Neurophysiol*. 2010;103(4):2275-2284. doi:10.1152/jn.00822.2009

161. Izawa J, Criscimagna-Hemminger SE, Shadmehr R. Cerebellar Contributions to Reach Adaptation and Learning Sensory Consequences of Action. *Journal of Neuroscience*. 2012;32(12):4230-4239. doi:10.1523/JNEUROSCI.6353-11.2012

162. Andreasen NC, Paradiso S, O'Leary DS. "Cognitive dysmetria" as an integrative theory of schizophrenia: A dysfunction in cortical-subcortical-cerebellar circuitry? *Schizophr Bull*. 1998;24(2):203-218. doi:10.1093/oxfordjournals.schbul.a033321

163. Andreasen NC, Nopoulos P, O'Leary DS, Miller DD, Wassink T, Flaum M. Defining the phenotype of schizophrenia: Cognitive dysmetria and its neural mechanisms. *Biol Psychiatry*. 1999;46(7):908-920. doi:10.1016/S0006-3223(99)00152-3

164. Andreasen NC, Pierson R. The Role of the Cerebellum in Schizophrenia. *Biol Psychiatry*. 2008;64(2):81-88. doi:10.1016/j.biopsych.2008.01.003

165. Clark S V., Tannahill A, Calhoun VD, Bernard JA, Bustillo J, Turner JA. Weaker Cerebellocortical Connectivity Within Sensorimotor and Executive Networks in Schizophrenia Compared to Healthy Controls: Relationships with Processing Speed. *Brain Connect*. 2020;10(9):490-503. doi:10.1089/brain.2020.0792

166. Moussa-Tooks AB, Kim DJ, Bartolomeo LA, et al. Impaired effective connectivity during a cerebellar-mediated sensorimotor synchronization task in schizophrenia. *Schizophr Bull*. 2019;45(3):531-541. doi:10.1093/schbul/sby064

167. Panouillères MTN, Joundi RA, Brittain JS, Jenkinson N. Reversing motor adaptation deficits in the ageing brain using non-invasive stimulation. *Journal of Physiology*. 2015;593(16):3645-3655. doi:10.1113/JP270484

168. Picard H, Amado I, Mouchet-Mages S, Olié JP, Krebs MO. The role of the cerebellum in schizophrenia: An update of clinical, cognitive, and functional evidences. *Schizophr Bull*. 2008;34(1):155-172. doi:10.1093/schbul/sbm049

169. Picard H, Le Seac'h A, Amado I, Gaillard R, Krebs MO, Beauvillain C. Impaired saccadic adaptation in schizophrenic patients with high neurological soft sign scores. *Psychiatry Res*. 2012;199(1):12-18. doi:10.1016/j.psychres.2012.04.039

170. Coesmans M, Röder CH, Smit AE, et al. Cerebellar motor learning deficits in medicated and medication-free men with recent-onset schizophrenia. 2014;39(1):3-11. doi:10.1503/jpn.120205

171. Rowland LM, Shadmehr R, Kravitz D, Holcomb HH. Sequential neural changes during motor learning in schizophrenia. *Psychiatry Res Neuroimaging*. 2008;163(1):1-12. doi:10.1016/j.pscychresns.2007.10.006

172. Scherer H, Bedard MA, Stip E, et al. Procedural Learning in Schizophrenia Can Reflect the Pharmacologic Properties of the Antipsychotic Treatments. *Cognitive and Behavioral Neurology*. 2004;17(1):32-40. doi:10.1097/00146965-200403000-00004

173. De Picker L, Ottoy J, Verhaeghe J, et al. State-associated changes in longitudinal [18F]-PBR111 TSPO PET imaging of psychosis patients: Evidence for the accelerated ageing hypothesis? *Brain Behav Immun*. 2019;77:46-54. doi:10.1016/j.bbi.2018.11.318

174. Doppelmayr M, Pixa NH, Steinberg F. Cerebellar, but not Motor or Parietal, High-Density Anodal Transcranial Direct Current Stimulation Facilitates Motor Adaptation. *Journal of the International Neuropsychological Society*. 2016;22(9):928-936. doi:10.1017/S1355617716000345

175. Telgen S, Parvin D, Diedrichsen J. Mirror Reversal and Visual Rotation Are Learned and Consolidated via Separate Mechanisms: Recalibrating or Learning De Novo? *Journal of Neuroscience*. 2014;34(41):13768-13779. doi:10.1523/JNEUROSCI.5306-13.2014

176. Heuer H, Hegele M. Age-related variations of visuo-motor adaptation beyond explicit knowledge. *Front Aging Neurosci*. 2014;6(JUL):1-12. doi:10.3389/fnagi.2014.00152

177. Fourneret P, De Vignemont F, Franck N, Slachevsky A, Dubois B, Jeannerod M. Perception of self-generated action in schizophrenia. *Cogn Neuropsychiatry*. 2002;7(2):139-156. doi:10.1080/13546800143000212

178. Christou AI, Miall RC, McNab F, Galea JM. Individual differences in explicit and implicit visuomotor learning and working memory capacity. *Sci Rep*. 2016;6:36633. doi:10.1038/srep36633

179. Tseng YW, Diedrichsen J, Krakauer JW, Shadmehr R, Bastian AJ. Sensory prediction errors drive cerebellum-dependent adaptation of reaching. *J Neurophysiol*. 2007;98(1):54-62. doi:10.1152/jn.00266.2007

180. Gallivan JP, Chapman CS, Wolpert DM, Flanagan JR. Decision-making in sensorimotor control. *Nat Rev Neurosci*. 2018;19(9):519-534. doi:10.1038/s41583-018-0045-9

181. Shergill SS, Samson G, Bays PM, Frith CD, Wolpert DM. Evidence for sensory prediction deficits in schizophrenia. *American Journal of Psychiatry*. 2005;162(12):2384-2386. doi:10.1176/appi.ajp.162.12.2384

182. Friston K, Brown HR, Siemerkus J, Stephan KE. The dysconnection hypothesis (2016). *Schizophr Res*. 2016;176(2-3):83-94. doi:10.1016/j.schres.2016.07.014

183. Friston K. Prediction, perception and agency. *Int J Psychophysiol*. 2012;83(2):248-252. doi:10.1016/j.ijpsycho.2011.11.014

184. Picard F, Friston K. Predictions, perception, and a sense of self. *Neurology*. 2014;83(12):1112-1118. doi:10.1212/WNL.0000000000000798

185. Apthorp D, Bolbecker AR, Bartolomeo LA, O'Donnell BF, Hetrick WP. Postural sway abnormalities in schizotypal personality disorder. *Schizophr Bull*. 2019;45(3):512-521. doi:10.1093/schbul/sby141

186. Bock O. Components of sensorimotor adaptation in young and elderly subjects. *Exp Brain Res*. 2005;160(2):259-263. doi:10.1007/s00221-004-2133-5

187. Willingham DB, Curran IT, Gabrieli J, Keane M, Proffit D. A Neuropsychological Theory of Motor Skill Learning. 1998;105:558-584.

188. Fitts PM. The information capacity of the human motor system in controlling the amplitude of movement. *J Exp Psychol*. 1954;47(6):381-391. doi:10.1037/H0055392

189. Jogems-Kosterman BJM, Zitman FG, Van Hoof JJM, Hulstijn W. Psychomotor slowing and planning deficits in schizophrenia. *Schizophr Res*. 2001;48(2-3):317-333. doi:10.1016/S0920-9964(00)00097-9

190. Docx L, Sabbe B, Provinciael P, Merckx N, Morrens M. Quantitative Psychomotor Dysfunction in Schizophrenia: A Loss of Drive, Impaired Movement Execution or Both? *Neuropsychobiology*. 2013;68(4):221-227. doi:10.1159/000355293

191. Janssens S, Moens H, Coppens V, et al. Psychomotor assessment as a tool to differentiate schizophrenia from other psychotic disorders. *Schizophr Res*. 2018;200:92-96. doi:10.1016/J.SCHRES.2017.06.047

192. Voelcker-Rehage C. Motor-skill learning in older adults-a review of studies on age-related differences. *European Review of Aging and Physical Activity*. 2008;5(1):5-16. doi:10.1007/S11556-008-0030-9/FIGURES/3

193. Bootsma JM, Caljouw SR, Veldman MP, Maurits NM, Rothwell JC, Hortobágyi T. Neural Correlates of Motor Skill Learning Are Dependent on Both Age and Task Difficulty. *Front Aging Neurosci*. 2021;13:643132. doi:10.3389/FNAGI.2021.643132/BIBTEX

194. Seidler RD, Bernard JA, Burutolu TB, et al. Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neurosci Biobehav Rev*. 2010;34(5):721-733. doi:10.1016/J.NEUBIOREV.2009.10.005

195. Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. *Schizophr Res*. 2004;72(1):29-39. doi:10.1016/J.SCHRES.2004.09.007

196. Kramer AO, Casaletto KB, Umlauf A, et al. Robust normative standards for the California Verbal Learning Test (CVLT) ages 60–89: A tool for early detection of memory impairment. *Clin Neuropsychol*. 2020;34(2):384. doi:10.1080/13854046.2019.1619838

197. Hill C, Van Gemmert AWA, Fang Q, Hou L, Wang J, Pan Z. Asymmetry in the aging brain: A narrative review of cortical activation patterns and implications for motor function. *https://doi.org/101080/1357650X20191707219*. 2019;25(4):413-429. doi:10.1080/1357650X.2019.1707219

198. Van Ruitenbeek P, Santos Monteiro T, Chalavi S, et al. Interactions between the aging brain and motor task complexity across the lifespan: balancing brain activity resource demand and supply. Published online 2022. doi:10.1093/cercor/bhac514

199. Heuer H, Hegele M. Generalization of implicit and explicit adjustments to visuomotor rotations across the workspace in younger and older adults. *J Neurophysiol*. 2011;106(4):2078-2085. doi:10.1152/JN.00043.2011

200. Lei Y, Wang J. The effect of proprioceptive acuity variability on motor adaptation in older adults. *Exp Brain Res*. 2018;236(2):599-608. doi:10.1007/S00221-017-5150-X/METRICS

201. Dong D, Yao D, Wang Y, et al. Compressed sensorimotor-to-transmodal hierarchical organization in schizophrenia. *Psychol Med*. 2023;53(3):771-784. doi:10.1017/S0033291721002129

202. Koshiyama D, Thomas ML, Miyakoshi M, et al. Hierarchical Pathways from Sensory Processing to Cognitive, Clinical, and Functional Impairments in Schizophrenia. *Schizophr Bull*. 2021;47(2):373-385. doi:10.1093/SCHBUL/SBAA116

203. Grootens KP, Vermeeren L, Verkes RJ, et al. Psychomotor planning is deficient in recent-onset schizophrenia. *Schizophr Res*. 2009;107(2-3):294-302. doi:10.1016/J.SCHRES.2008.09.032

204. Bervoets C, Docx L, Sabbe B, et al. The nature of the relationship of psychomotor slowing with negative symptomatology in schizophrenia. *Cogn Neuropsychiatry*. 2014;19(1):36-46. doi:10.1080/13546805.2013.779578

205. Morrens M, Hulstijn W, Matton C, et al. Delineating psychomotor slowing from reduced processing speed in schizophrenia. *http://dx.doi.org/101080/13546800802439312*. 2008;13(6):457-471. doi:10.1080/13546800802439312

206. Docx L, Morrens M, Bervoets C, et al. Parsing the components of the psychomotor syndrome in schizophrenia. *Acta Psychiatr Scand*. 2012;126(4):256-265. doi:10.1111/J.1600-0447.2012.01846.X

207. Thomassen AJWM, Meulenbroek RGJ, Tibosch HJCM. Latencies and kinematics reflect graphic production rules. *Hum Mov Sci*. 1991;10(2-3):271-289. doi:10.1016/0167-9457(91)90007-K

208. Jogems-Kosterman BJ, Zitman FG, Van Hoof JJ, Hulstijn W. Psychomotor slowing and planning deficits in schizophrenia. *Schizophr Res*. 2001;48(2-3):317-333. Accessed August 31, 2014. http://www.ncbi.nlm.nih.gov/pubmed/11295384

209. Rosenbaum DA. Knowing Hands: The Cognitive Psychology of Manual Control. *Knowing Hands*. Published online February 27, 2017. doi:10.1017/9781316148525

210. Rosenbaum DA, Feghhi I. The time for action is at hand. *Atten Percept Psychophys*. 2019;81(7):2123-2138. doi:10.3758/s13414-018-01647-7

211. Izawa J, Criscimagna-Hemminger SE, Shadmehr R. Cerebellar Contributions to Reach Adaptation and Learning Sensory Consequences of Action. *Journal of Neuroscience*. 2012;32(12):4230-4239. doi:10.1523/JNEUROSCI.6353-11.2012

212. Andreasen NC. Clinical research. Published online 2008:251-255.

213. Van Erp TGM, Preda A, Nguyen D, et al. Converting positive and negative symptom scores between PANSS and SAPS/SANS. *Schizophr Res*. 2014;152(1):289-294. doi:10.1016/J.SCHRES.2013.11.013

214. Pieters LE, Deenik J, Tenback DE, Van Oort J, Van Harten PN. Exploring the Relationship between Movement Disorders and Physical Activity in Patients with Schizophrenia: An Actigraphy Study. *Schizophr Bull*. 2021;47(4):906-914. doi:10.1093/schbul/sbab028

CURRICULUM VITAE

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CURRENT POSITION

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Clinical activities:

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- *Department for people with intellectual disabilities 'Knoop 2B'*
- *Ambulatory care*

PhD researcher in Medical Sciences 1/8/2013 – today
Collaborative Antwerp Psychiatric Research Institute (CAPRI), University of Antwerp, Belgium
SINAPS, Research Unit of University Psychiatric Hospital, Duffel, Belgium
PhD project: Motor Learning in Schizophrenia and Ageing – two different patterns of decline

Principal investigator 7/11/2023 – today
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ACADEMIC DEGREE

Master of Specialist Medicine – Adult Psychiatry 1/8/2013-31/1/2020
University of Antwerp
Master's thesis: Sensomotorisch leervermogen bij schizofrenie en normale veroudering

Master of Medicine 2006-14/6/2013
University of Antwerp
Master's thesis: "Evaluatie van de bovenste luchtweg in de oppuntstelling voor tandheelkundige en chirurgische behandeling bij patiënten met obstructief slaapapneu"

RESEARCH EXPERIENCE – INVOLVEMENT IN CLINICAL TRIALS

NOCOMPOUNDEDI0004 (Phase 0): "An Exploratory Study to Measure and Contrast Implicit and Explicit Learning Performance in Patients with Stable Schizophrenia and Young and Elderly Healthy Subjects", Janssen Research and Development, 2012-2013. ClinicalTrials.gov identifier: NCT01788436 - *Study investigator*

KETIVEDI2001 (Phase IIa): "An exploratory blinded, randomized, placebo-controlled study in patients with major depressive disorder to investigate the effect of minocycline on relapse after successful IV ketamine-induced (partial) symptom resolution", Janssen Research and Development, 2013. ClinicalTrials.gov identifier: NC01809340; EudraCT number: 2012-002954-21 - *Study investigator*

EULAST: "EUropean Long-acting Antipsychotics in Schizophrenia Trial, Comparing Outcome in Schizophrenia between Different Depot Antipsychotics and Oral Medication". Eudra-CT-Number: 2014-002765-30. – *Study investigator*

CONNEX 3: "A phase III randomized, double-blind, placebo-controlled parallel group trial to examine the efficacy and safety of BI 425809 once daily over 26-week treatment period in patients with schizophrenia." ClinicalTrials.gov identifier: NCT04860830. Boehringer Ingelheim – *Principal investigator*

67953964MDD3007: "A Randomized, Double-Blind, Multicenter, Placebo-controlled Study to Evaluate the Efficacy of Aticaprant X mg as Adjunctive Therapy in Adult Participants with Major Depressive Disorder with Prominent Anhedonia (MDDANH+) and Inadequate Response to Current Antidepressant Therapy." Janssen Research and Development – *Principal investigator*

67953964MDD3005: "A Randomized, Double-Blind, Multicenter, Placebo-Controlled Study of Adjunctive Aticaprant plus an Antidepressant (SSRI / SNRI) for Relapse Prevention in Major Depressive Disorder with Anhedonia Symptoms." Janssen Research and Development – *Principal investigator*

ORAL PRESENTATIONS

"**Interactieve infosessie: De Toren nodigt uit; Wetenschappelijk onderzoek ontsluierd**", 3/10/2013, Psychiatric Hospital Duffel (conference center 'De Kleiput'), Belgium

"**Handschriftverkleining als innovatief hulpmiddel voor de adequate dosering van antipsychotica bij de behandeling van schizofrenie"**, 15/10/2013, CAPRI Research Club, University of Antwerp (Campus Drie Eiken)

"A Short introduction to The Learning Curves", 4/2014, AKS, University Psychiatric Hospital Duffel

"Is schizofrenie een vroegtijdig dementieel syndroom?", 17/9/2013, 7de Vlaams GGZ congres, University of Antwerp (Campus Drie Eiken)

"Leervermogen gemeten door middel van de Symbol Digit Substitution Task", 6/10/2014, AKS, University Psychiatric Hospital Duffel

"Preserved SDST learning in schizophrenia", 31/3/2015, European Psychiatric Association congress, Vienna, Austria

"**Impaired implicit sequence learning in schizophrenia after more advanced training of a spatial motor task"**, BCNBP Research in Psychiatry Day, Leuven, Belgium, 2/10/2015

"Is onbewust leervermogen aangetast bij schizofrenie?", 15/12/2015, CAPRI Research Club, University of Antwerp (Campus Drie Eiken)

"Eerste psychose, differentieel diagnose en psychosociale interventies bij psychose", 11-12/2015, University of Antwerp, Campus Drie Eiken

"**Comparing schizophrenia and elderly on implicit sequence learning: A similar deficit after extensive training may be related to different mechanisms**", 30/3/2016, Conference on cognitive neuropsychiatry: Self disorders in schizophrenia, Strasbourg, France

Postgraduaat "**Sensomotorisch leervermogen bij schizofrenie en normale veroudering"**, 5/11/2019, University Hospital Antwerp, Belgium

"Schizofrenie, een vorm van versnelde veroudering?", 2/3/2021, Lokale Kwaliteitsgroep Psychiatrie, Antwerp, Belgium

PUBLICATIONS

Publications in peer reviewed journals

A1 publications included in the dissertation

Cornelis, C., De Picker, L. J., Hulstijn, W., Dumont, G., Timmers, M., Janssens, L., … Morrens, M. (2014). **Preserved learning during the Symbol Digit Substitution Test in patients with schizophrenia, age-matched controls and elderly**. Frontiers in Psychiatry, 5. http://doi.org/10.3389/fpsyt.2014.00189

De Picker, L. J., Cornelis, C., Hulstijn, W., Dumont, G., Fransen, E., Timmers, M., … Sabbe, B. G. C. (2014). **Stable schizophrenia patients learn equally well as age-matched controls and better than elderly controls in two**

sensorimotor rotary pursuit tasks. Frontiers in Psychiatry, 5, 165. http://doi.org/10.3389/fpsyt.2014.00165

Cornelis, C., De Picker, L. J., De Boer, P., Dumont, G., Coppens, V., Morsel, A., … Hulstijn, W. (2016). **Implicit motor sequence learning in schizophrenia and in old age: reduced performance only in the third session.** Experimental Brain Research. http://doi.org/10.1007/s00221-016-4751-0

Cornelis C., De Picker L.J., Coppens V., Morsel A., Timmers M., Dumont G., Sabbe B.G.C., Morrens M., Hulstijn W. (2022). **Impaired Sensorimotor Adaption in Schizophrenia in Comparison to Age-Matched and Elderly Controls.** Neuropsychobiology. 2022;81(2):127-140. http://doi.org/10.1159/000518867

Other A1 publications

Cornelis, C. (2014). **Referaat: Interpersoonlijke therapie versus SSRI's in de behandeling van een eerste of tweede depressie**. http://www.tijdschriftvoorpsychiatrie.nl/assets/articles/56-2014-11-artikel-cornelis.pdf

Cornelis, C., Van Gastel, A., Dumont, G., Coppens, V., Sabbe, B., Morrens, M., & Van Den Eede, F. (2016). **A case of dose escalation of quetiapine in persistent insomnia disorder.** Acta Clinica Belgica, 1–3. http://doi.org/10.1080/17843286.2016.1252546

Hulstijn W., Cornelis C., Morsel A., Timmers M., Morrens M., Sabbe B.G.C. **Motor learning and performance in schizophrenia and aging: two different patterns of decline**. (2024). Experimental Brain Research. https://doi.org/10.1007/s00221-024-06797-9

Other publications

Cornelis, C., Dumont, G., Sabbe, B. **Schizofrenie: het groeiend neurowetenschappelijke inzicht**. Antwerps Farmaceutisch Tijdschrift, vol. 7 (2014)

DEDICATIONS AND ACKNOWLEDGEMENTS

‘Hitting the target’ is een veelvoorkomende Engelse uitdrukking die in diverse contexten wordt gebruikt. Het kan verwijzen naar het bereiken van doelen met motorische precisie en nauwkeurigheid. In deze thesis slaat deze titel enerzijds op de ogenschijnlijk eenvoudige taken waarmee onze deelnemers werden geconfronteerd: het bereiken van doelen op een digitale schrijftablet met een pen. Deze eenvoudige oefening bevat essentiële informatie om diepgaande inzichten te verkrijgen in complexe leerprocessen en de motorische vertraging bij schizofrenie. Anderzijds heb ik voor deze titel gekozen omdat deze doctoraatsverdediging voor mij de verwezenlijking is van een langverwachte doelstelling. Ik ben zeer blij en dankbaar dat ik mede dankzij onderstaande mensen dit werk heb kunnen afronden en vandaag mag presenteren. Een van de quotes van mijn pianoleraar, Peter Van der Koelen, was: "Il faut reculer pour mieux sauter." Het is belangrijk om wat te vertragen alvorens een uitdagende passage te beginnen spelen. Deze uitdrukking is voor mij niet alleen van toepassing in de muziek. Ook hier had ik een pauze nodig om met meer mentale ruimte en maturiteit de laatste loodjes van dit proefschrift af te werken.

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