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Investigations of differences in verbal and visual learning impairment in schizophrenia spectrum disorders, using traditional and novel learning metrics

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Abstract

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Title: Investigations of differences in verbal and visual learning impairment in schizophrenia spectrum disorders, using traditional and novel learning metrics

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Background: Learning impairment in schizophrenia spectrum disorders are at the core of the disorder and have been studied variously in comparison to healthy controls. The current study aims to investigate verbal and visual learning impairment, by comparing Hopkins Verbal Learning Test-Revised (HVLT-R) and Brief Visuospatial Memory Test-Revised (BVMT-R) performances of patients with schizophrenia and healthy controls. The groups are compared on the traditional measures of learning curves (LC), and raw learning score measures (RLS), along with the novel learning ratio (LR) metric. Additionally, interaction effects of demographic variables were investigated to eliminate possible confounds.

Methods: As part of the cognitive assessment for the Thematically Organized Psychosis (TOP) study at the Norwegian Centre for Mental Disorders Research (NORMENT), 179 patients with schizophrenia and 658 healthy controls completed HVLT-R and BVMT-R. Demographic variables such as age, IQ and education were assessed. Data was analysed using GLM repeated measures ANOVA, independent samples T-tests and multivariate ANOVA.

Results: The patients with schizophrenia demonstrated inferior performance in all cognitive measures in comparison to healthy controls. The superiority of visual and verbal learning performance in healthy controls was present both when using the traditional methods LC, and the novel LR metric. In contrast to LR and LC, the RLS did not prove useful in detecting differences in learning ability, in either of the groups.

Conclusion: As hypothesised, schizophrenia performed significantly poorer than healthy controls in verbal and visual learning, which supports previous literature. The LR metric proved sensitive to learning capacity deficits in schizophrenia, which is novel findings to the best of found knowledge.

Preface

This thesis is based on data from the Thematically Organized Psychosis (TOP) study at the Norwegian Centre for Mental Disorders Research (NORMENT). During my employment of four years at NORMENT as a research assistant, I have partaken in the cognitive assessment of healthy controls at the Cognitive Core Resource Unit, led by my supervisor Torill Ueland.

I would like to humbly thank my conversant supervisors Nils Inge Landrø and Torill Ueland for guidance and academic discussions. I am grateful to their patience, sagacious advice, and proofreading.

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Lastly, I would like to thank my loving and supportive family and friends, for their faith in me, their patience with me, and their long-lasting encouragement. I want to extend my gratitude especially to my father and my grandmother.

Oslo, October 2022

Sandra Aakjær Bruun

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1. Introduction

Schizophrenia spectrum disorders have been investigated in various interdisciplinary ways since it was established as a disorder. To this day, the disorder is known to puzzle researchers and many answers are still left to be answered. Research has established that cognitive dysfunction is a core feature of schizophrenia (Green et al., 2019). Amongst the most consistently found cognitive impairments is learning, which this thesis will explore.

1. 2 Schizophrenia

In the early pioneering work of schizophrenia research, Kraepelin and Barclay (1919) viewed it as a multifactorial disorder interacting with internal and external causes (Kraepelin & Barclay, 1919). Because schizophrenia was viewed as a neurodegenerative disorder in line with dementia, it was named dementia praecox. Insel (2010) states that the manifestations of the disorder have changed little over the past century and provides the following clarifying definition of schizophrenia in his review:

> Schizophrenia is a syndrome: a collection of signs and symptoms of unknown aetiology, predominantly defined by observed signs of psychosis. In its most common form, schizophrenia presents with paranoid delusions and auditory hallucinations late in adolescence or early adulthood. (Insel, 2010, p. 187)

Schizophrenia is a disorder with an estimated lifetime prevalence of about 1% of the world's population that cuts across cultures, regions, and gender, while psychosis more broadly is estimated to impact roughly 3% of the population (McCleery & Nuechterlein, 2019). Schizophrenia, therefore, arguably is the most severe and persistent psychotic illness. Affected individuals experience global generalised disabilities, such as decreased somatic health, low employment rates, educational achievement, and reduced quality of life and life expectancy (Schaefer et al., 2013; Toulopoulouand & Murray, 2004). The symptoms of schizophrenia are commonly classified into positive, negative, and disorganised symptoms. This symptom differentiation was derived from Bleuler's (1950) two types of symptoms, the fundamental (of cognitive nature) and the accessory (positive symptoms) (Bleuler, 1950; Green & Harvey, 2014; Harvey, 2013). He described the discrepancy between fundamental psychotic symptoms, and the patient's incapability of holding their train of thought, and thereby intuitively understood that cognitive impairment was a core feature, which has

widened our modern understanding of schizophrenia (Bleuler, 1950). Bleuler outlined cognitive dysfunction as an important feature of schizophrenia, which remains focal to contemporary schizophrenia research.

1.2.2 Cognition in schizophrenia

Schizophrenia is regarded as a complex disorder with widespread cognitive impairments (Rund, 2016; Rund, 2018). For decades, cognitive impairment has been regarded as a prominent core feature of schizophrenia (Green, 1996; Green & Harvey, 2014; Harvey, 2013; Heinrichs & Zakzanis, 1998; Insel, 2010; Nuechterlein et al., 2004).

Empirical reviews consistently show markedly impaired performance across a wide range of cognitive tests and domains in schizophrenia, with mean effect sizes in the large range (Albus et al., 2019; Fett et al., 2020; Green et al., 2019; Heinrichs & Zakzanis, 1998; McCleery & Nuechterlein, 2019; Schaefer et al., 2013). Schaefer et al. (2013) reported significant findings from publications between 1980-2006 of generalised cognitive impairment in schizophrenia that remained robust over time, in different regions of the world (Schaefer et al., 2013). This was recently supported by Fett et al. (2022) who reviewed findings of a global cognitive decline in schizophrenia compared to healthy individuals and found more severe decline in schizophrenia than in healthy controls. In the review of McCleery and Nuechterlein (2019) they established that impaired cognition impacts are diffuse, as it can be found across many cognitive domains. As Green (1996) stated early on, the cognitive deficits contribute to the social disability associated with the disorder, and to the high burden of the disease over the course of the illness (Green, 1996).

When compared to healthy controls, the most commonly reported impaired cognitive domains in schizophrenia are; working memory (Aleman et al., 1999; Mesholam-Gately et al., 2009), verbal learning (Mesholam-Gately et al., 2009), visual learning and reasoning/problem solving (Zhang et al., 2017), processing speed (Knowles et al., 2010), attention and vigilance (McCleery et al., 2015), and social cognition (Vaskinn et al., 2022). As a group, patients with schizophrenia show marked impairment with performance ranging from about 0.75 to 1.7 standard deviation (SD) below the performance of healthy control samples (Albus et al., 2019; Heinrichs & Zakzanis, 1998; Kern et al., 2011; Mesholam-Gately et al., 2009). This indicates a generalised cognitive impairment in schizophrenia.

In early research it was established that participants with schizophrenia perform inferior to age-matched controls on measures of verbal memory, executive functioning, attention, and processing speed (Heinrichs & Zakzanis, 1998). Verbal deficits appear early in the course of the disorder and are relatively stable (Heinrichs & Zakzanis, 1998; Mesholam-Gately et al., 2009; Mollon & Reichenberg, 2018), while impairments in processing speed and executive functions increase during adolescence (Mollon & Reichenberg, 2018). When comparing schizophrenia and healthy controls, McCleery and Nuechterlein (2019) reported relatively greater impairment in speed of processing and working memory domains, and relatively less impairment for reasoning and problem solving. Notably, when assessing memory and processing speed, effect sizes have tended to be slightly larger (Heinrichs & Zakzanis, 1998; Schaefer et al., 2013), often with most pronounced impairments in verbal memory and processing speed (Mesholam-Gately et al., 2009). In some studies impairments in executive functions seem stand out in schizophrenia, in comparison to healthy controls (Heilbronner et al., 2016; Haatveit et al., 2015). Reichenberg et al. (2009) found that schizophrenia patients were more impaired than the other groups in memory, executive functions, and attention and processing speed, in their study of cognitive impairment across diagnostic subgroups of psychosis disorders. More recent evidence points to a continuum of cognitive impairments in psychotic disorders: the most severe in schizophrenia, intermediate impairment in bipolar disorder, and the least severe in psychotic depression (Sheffield et al., 2018).

In a systematic review of cognitive subgroups in schizophrenia by Carruthers et al. (2019), they established three distinct cognitive subgroups from their review of 52 studies from 1980 to 2019. The three groups consisted of a relatively intact cognitive subgroup characterised by high cognitive performance, an intermediate cognitive subgroup defined by mixed moderate levels of cognitive function/dysfunction, and a globally impaired subgroup characterised by severe cognitive deficits (Carruthers et al., 2019). Similarly, Vaskinn et al. (2020) conducted a cluster analysis of cognitive heterogeneity schizophrenia and identified three cognitive subgroups, a relatively intact group (36%), an intermediate group with mild cognitive impairment (44%), and an impaired group with globally impaired cognition (20%) (Vaskinn et al., 2020). It is worth noting that around 30% of individuals with schizophrenia perform within the normal range of cognitive functioning (Fett et al., 2022; Harvey, 2013; Heinrichs & Zakzanis, 1998), in the absence of clinically significant cognitive impairment. However, in a study comparing cognitive performance with expectations based on estimates of the individual's premorbid level of intellectual functioning (IQ), patients with schizophrenia performed at a level below what would be expected if healthy (Vaskinn et al., 2014).

Lastly, recent studies have shown that intellectual functioning was lower in patients with schizophrenia when compared to healthy controls (Flaaten, Melle, Gardsjord, et al., 2022), and that 70% of patients with schizophrenia showed deterioration of IQ, following the onset of the disorder (Ohi et al., 2017)

1.1.3 Timing and course of cognitive impairment in schizophrenia

For several decades researchers have examined cognitive impairment across different illness phases of schizophrenia. The timing of cognitive impairment during the illness course has been investigated to elucidate whether cognitive impairments present at the onset of psychosis or precede the onset of psychosis. Most studies investigate people with ultra-high-risk (UHR) of developing psychosis (with either first-degree relatives of schizophrenia or individuals putatively prodromal for a psychotic illness), first-episode (FEP) patients, or patients with chronic (CH) schizophrenia.

Research suggest that cognitive impairments predate psychosis onset (Fusar-Poli et al., 2012), and are present before other symptoms of schizophrenia occur (Reichenberg et al., 2009). Several meta-analyses have found compromised patterns of cognitive functioning in UHR individuals, prior to the onset of overt psychosis (Bang et al., 2015; Bortolato et al., 2015; Fusar-Poli et al., 2012; Green et al., 2019). But effect sizes of cognitive impairments seem to vary in magnitude. Fusar-Poli et al. (2012) found small to medium effect sizes of cognitive impairment in studies of UHR individuals. They found impairments in both working memory, verbal fluency, verbal memory, processing speed, attention, visual memory, executive functioning, social cognition, and general intelligence (Fusar-Poli et al., 2012). Bang et al. (2015) observed in that the effect sizes of cognitive impairment across domains tend to be smaller in UHR individuals, than in FEP patients and chronic patients.

A 2-year follow-up study found that baseline cognitive impairment was especially severe among UHR individuals, when comparing cognitive performance to healthy controls (Lam et al., 2018). Another study that also compared UHR individuals to healthy controls and found that UHR individuals significantly differed in verbal learning and memory, speed of processing, and overall composite score, from healthy controls (Carrión et al., 2018). Also, they found no direct indications of a cognitive decline from the high-risk state to the onset of the first episode.

Bang et al. (2015) suggested that early neurodevelopmental factors may play a role in the transition in UHR to overt psychosis, and that there could be different developmental

trajectories between converters and non-converters. This is supported by Melle (2019) who writes that “the widening gap towards healthy adolescence, can be explained by a developmental lag rather than a loss of acquired functions” (Melle, 2019, p. 165). This has recently been corroborated by Mohn-Haugen et al. (2022). They found that impairments in mental processing speed, visuospatial abilities, and visual working memory manifest as developmental lag and become more significantly impaired later in life (Mohn-Haugen et al., 2022).

Several reviews support found profound cognitive impairment present at the onset of schizophrenia, but no progressive cognitive deterioration after the onset of the illness (Becker et al., 2010; Bortolato et al., 2015; Carrión et al., 2018; Green, Kern, et al., 2004; Mesholam-Gately et al., 2009). Results from the study of Mesholam-Gately et al. (2009) showed impairments in FEP patients with large effect sizes mainly in verbal memory, nonverbal memory, working memory, processing speed, language, executive functioning, attention/vigilance, motor skills, and social cognition (Mesholam-Gately et al., 2009). Cognitive deficits seem to be present in pre-morbid stages of the disorder, before the prodromal phases of psychosis, and show stabilisation of cognitive impairment after the onset of psychosis (Albus et al., 2019; Bergh et al., 2016; Haatveit et al., 2015; Keefe et al., 2006; Rund et al., 2016). This has also been corroborated by several longitudinal studies of FEP patients. In a meta-analysis of longitudinal studies of UHR individuals and FEP patients by Bora & Murray (2014), no evidence was found of critical cognitive decline before the onset of psychosis in patients with UHR individuals and FEP patients. In contrast, they found improved cognitive performances of both UHR individuals and FEP patients at follow-up timepoints (Bora & Murray, 2014). In the prospective 15-year follow-up study of FEP patients by Albus et al. (2019), FEP patients showed stable and widespread cognitive deficits compared to healthy controls, at both baseline and at 15-year follow-up. The 10-year follow-up study by Bergh et al., (2016) reported stability of cognitive performance with no significant change in set-shifting, design fluency, processing speed, and verbal fluency. Rund et al. (2016) suggested that early clinical course was a good predictor for cognitive functioning in schizophrenia, as they found no evidence of cognitive deterioration in their Norwegian 10-year follow-up study of FEP patients (Rund et al., 2016). Both long-term stability and modest increases in cognition over time, was found in a more recent Norwegian 10-year follow-up study of FEP patients, as well as indications of deterioration in with poor baseline performance (Flaaten, Melle, Bjella, et al., 2022). A smaller-scale Norwegian follow-up study also supported the stability of cognition over 10 years in FEP patients (Barder et al.,

2013). These findings suggest distinct patterns of cognitive impairments in schizophrenia over time.

A growing number of longitudinal studies find cognitive deficits to persist during the entire course of the illness after the onset of psychosis (Albus et al., 2019; Becker et al., 2010; Becker et al., 2021; Fu et al., 2018; Rodríguez-Sánchez et al., 2013; Rodríguez-Sánchez et al., 2008; Rund et al., 2016). In a 20-year follow-up, some cognitive function was found to be stably impaired in FEP patients after onset of the illness (Bonner-Jackson et al., 2010). In an extensive longitudinal study, Fett et al. (2020) of a first-admission psychosis cohort found that most cognitive functions declined over 2 decades after first hospitalization. The cognitive performances declined over time, and the cognitive impairments predicted worse vocational functioning 18 years after onset of the illness. Specifically, verbal memory, visual memory, attention and processing speed, and abstraction-executive function showed changes greater than expected from to normal aging (Fett et al., 2020).

Several longitudinal and cross-sectional studies have found evidence of greater heterogeneity in cognitive impairment in schizophrenia initially at onset of psychosis, and reduced heterogeneity after stabilisation of the disorder (Albus et al., 2019; Becker et al., 2010; Carrión et al., 2018; Fett et al., 2020; Fu et al., 2018; Rodríguez-Sánchez et al., 2013; Rund et al., 2016). This points to a diverse understanding of the cognitive course of schizophrenia, and of schizophrenia as a disorder. Furthermore, studies have found cognitive abnormalities to be manifested already in adolescence (Mohn-Haugen et al., 2022), and even found improvements after the onset of psychosis (Insel, 2010; Owen et al., 2011; Rund, 2009; Weinberger, 2017). There is even evidence of symptomatic remission and early clinical recovery in 26% of FEP patient in a 1-year follow-up study (Simonsen et al., 2017). In total, longitudinal studies do not seem to support progressive deterioration of cognition during the transition between the early and chronic phases of the disorder (McCleery & Nuechterlein, 2019). Also, the course of the disorder in cognitive impairments seem to be heterogenic and stabilise after onset.

From the presented findings, extensive evidence states that cognitive impairments are core features in schizophrenia throughout the course of the disorder. This gives insights to better understanding of prognosis and heterogeneity of diagnosis. This was recently pointed out by Catalan et al. (2021) in comprehensive meta-analysis of UHR and healthy controls. They found significant differences between the two groups on tests of cognition to an extend that they suggest cognitive dysfunction as a potential marker for diagnosis and prognosis (Catalan et al., 2021).

1.4.5 Learning and memory

Memory is among the essential cognitive abilities assessed during neuropsychological testing and is impacted by our learning skills (Lezak et al., 2012). Memory functions are commonly divided into two different systems: declarative (explicit) and non-declarative (implicit) memory. Explicit memory is knowledge of events, facts, and objects, and implicit is more performance-based, such as learning. Further, we have short-term memory with a limited amount of storage and temporal duration and long-term memory, which refers to unlimited capacity unrestrictive to temporal duration and storage (Lezak et al., 2012).

We have three main stages of memory information (Toulopoulouand & Murray, 2004). Encoding is an active organisation of material to be learned, which affects immediate recall. Storage is the consolidation of information encoded, which essentially can be evaluated as rate-of-forgetting by calculating the percentage of retained information after the first trial about the second trial. Retrieval refers to a process of recollecting or reassessing stored information (Toulopoulouand & Murray, 2004).

1.4.1 Learning and memory impairments in schizophrenia

Green (1996) stated that cognitive deficits in people with schizophrenia restrict them in their ability to retain, acquire or re-learn skills (Green, 1996). This has since been corroborated in several studies. A meta-review by Aleman et al. (1999) revealed a significant and stable association between schizophrenia and memory impairment (Aleman et al., 1999). In a 5-year follow up study, Gold et al. (2000) first found that immediate recall improved, and later found impairments in immediate recall as a primary deficit in initial requisition on information (Gold et al., 2000). This suggests that the primary deficit is in the initial acquisition of information, rather than an increase in forgetfulness. Further, in the study of Foley et al. (2008), chronic schizophrenia patients appear to have impairment patterns similar to patients with cortical dementia, and poorer learning and memory function than healthy controls (Foley et al., 2008). They suggested that deficits might be in immediate encoding, rather than memory decay for some types of memory ability. Taken together, growing evidence is showing complex deficits in various memory processes. In the following,

evidence of verbal and visual learning impairment in schizophrenia will be presented, to elaborate on this.

1.5.2 Verbal and visual learning impairments in schizophrenia

As Green et al. (2019) simply put it, verbal learning and memory refers to the initial encoding, subsequent recall, and recognition of words, involving language. Similarly, visual learning and memory involves the initial encoding, subsequent recall, and recognition of information such as colour, shape, and location (Green et al., 2019). Early on, Heinrich & Zakzanis (1998) found that schizophrenia patients mainly scored significantly lower than healthy controls on verbal memory, visual memory, along with attention (Heinrichs & Zakzanis, 1998). Longitudinal studies have shown that, when compared to healthy controls, patients with schizophrenia can exhibit improvement in cognitive impairments, except for verbal memory (Addington et al., 2005; Carrión et al., 2018; Fu et al., 2018; Mesholam-Gately et al., 2009; Mohn & Torgalsbøen, 2018; Rodríguez-Sánchez et al., 2013; Rodríguez-Sánchez et al., 2008; Schaefer et al., 2013; Seidman et al., 2016; Vesterager et al., 2012). A recent longitudinal study by Fett et al. (2020), however, found that performance in verbal and visual memory, as well as in attention, declined over time in their 18-year follow-up study. Both these perspectives point to presence of impairments in schizophrenia over the course of the illness, but with divergent patterns in verbal and visual memory (Fett et al., 2020).

Studies regarding verbal memory show various results, indicating smaller differences, no differences, or larger changes in FES-patients, than healthy controls. When addressing FEP patients, they slightly deteriorated in verbal learning by 5-year follow-up, whilst controls improved (Albus et al., 2006). Further, in the long-term study of Zanelli et al. (2019) schizophrenia participants exhibited verbal memory decline after illness onset in comparisons to healthy controls (Zanelli et al., 2019). Interestingly, in the study of Torgalsbøen et al. (2015), patients with schizophrenia showed decline on verbal learning at the 2-year follow-up, but when completing a 6-year follow up of the same sample, Fu et al. (2018) found no differences in verbal memory. This suggest that these cognitive changes are only temporary, as verbal learning proved to improve after two years. Simultaneously, cognitive trajectory for verbal learning showed a larger improvement for the patient group than for the control group over time (Fu et al., 2018).

In FEP patients, cognitive impairments have been found to be mainly global, but with subtle impairments in verbal and visual memory (Toulopoulouand & Murray, 2004). This has

been corroborated in other studies and is an important contribution to the understanding of symptoms preceding onset of psychosis. A study found that verbal learning was the strongest predictor of schizophrenia, as a relative decline in verbal ability was present already between from the ages 13 and 18 in a study of UHR adolescence (MacCabe et al., 2013). Thus, decline in verbal learning was associated with increased risk for psychosis in adulthood. In a recent comprehensive study, the strongest evidence for impairment pre-onset was for verbal learning and memory, as well as executive function, mental processing speed, and social cognition (Mohn-Haugen et al., 2022). In a meta-analysis it was even suggested that verbal learning impairments predict transition to psychosis, from their results showing that verbal learning and memory impairments were present in UHR individuals, and had the largest effect sizes (Bang et al., 2015).

Verbal memory seems to be a predictor of functional outcome (Green et al., 2019), as impairments is found in FEP patients (Toulopoulouand & Murray, 2004). A study investigating cognition and occupational functioning demonstrated significant correlations between all tested cognitive domains and vocational functioning at the beginning of vocational rehabilitation, except from verbal learning (Lystad et al., 2017). They attributed this finding to the variety of cognitive functioning at work. This is interesting when considering the effect of vocational rehabilitation and cognitive remedy therapies, knowing that verbal learning seems to hold a gate-keeper function.

It is not well known what exactly cause these verbal learning deficits or inferior test performances. However, Cirillo and Seidman (2003) concluded that impaired verbal memory could be mainly attributed to a deficit in the encoding stage, and thereby affecting learning processes, with an increase in forgetfulness in schizophrenia (Cirillo & Seidman, 2003). This is contrary to the previously mentioned suggestion from Gold et al. (2000). The study of Hill et al. (2004) showed that on measures of verbal learning, short- and long-term memory, and immediate attention, antipsychotic-naïve FEP schizophrenia performed significantly worse than healthy controls. They attributed the verbal learning deficits to recall and reduced use of organisational strategies to facilitate verbal encoding and retrieval (Hill et al., 2004). Recent findings showed that verbal learning is impaired in both initial recall and learning rate in FEP (Egloff et al., 2018). Semantic encoding strategy was a significantly stronger predictor of overall verbal learning for schizophrenia compared to healthy controls in the study of Hill et al. (2004). Semantic encoding strategies was critical to performance of verbal learning. Which essentially means that schizophrenia seem to manifest verbal memory deficits if failing to semantically organize verbal information (Hill et al., 2004). Recently, results showed that

patients with schizophrenia experience perceptual deficits in processing auditory and visual stimuli (Green et al., 2019). The presented findings of complex deficits in verbal learning seem somewhat unique to individuals with schizophrenia, when compared to healthy controls.

Visual learning and memory in schizophrenia has not been investigated as extensively as verbal learning and memory (Green & Harvey, 2014). However, several studies have found various results of visual learning impairments in schizophrenia. Albus et al. (2002) observed visual memory impairments FEP patients, that appeared to be stable after a 2-year follow-up period. In the same study, healthy controls and FEP patients both showed improvements in visual learning at follow-up, but healthy controls were superior in performance (Albus et al., 2002). Mohn and Torgalsbøen (2018) found a modest improvement in visual learning in a 2-year follow-up study of FEP patients (Mohn & Torgalsbøen, 2018), supporting the findings of (Tracy et al., 2001). Although, in the study by Mohn and Torgalsbøen (2018), the patients performed significantly deficient at both baseline and follow-up compared to the healthy controls. Relative improvement in visual learning over a period of 10-year follow-up was found in patients with schizophrenia, when compared to controls (Hoff et al., 2005). The patients improved more than controls on a measure of immediate visual memory. An interesting finding is the statistically significant group by time interaction, when interpreting the change in visual impairment (Fu et al., 2018; Hoff et al., 2005).

Verbal and visual memory have been found to be the most impaired domains in UHR individuals who transitioned to psychosis later in the course of their illness (Fusar-Poli et al., 2012). These showed greater impairment compared to UHR individuals who did not transition to psychosis during the respective follow-up periods. This was later supported by Carrión et al. (2018). With this, it suggests a relative deterioration for patients with schizophrenia in visual learning impairment, which appear consistent as a clinical characteristic of schizophrenia.

All together, these findings presented encompasses an understanding of superiority of verbal impairments, in the cognitive domains of learning and memory in schizophrenia. This reflects the necessity of having a control group in follow-up studies, to separate effect from repeated practice and absolute change in patients from healthy controls. Nevertheless, visual learning and memory is of relevance and importance in the informing of clinical presentation of schizophrenia.

1.3 MATRICS

Up until more recent years, there was no consensus on a standard way to define critical domains of cognitive impairments in schizophrenia (Green & Harvey, 2014). The National Institute of Mental Health (NIHM) initiative, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) was launched in 2004 (Marder & Fenton, 2004). The purpose of the initiative was to develop a consensus cognitive battery which could be used in studies pharmacological interventions of cognitive enhancement for schizophrenia (Nuechterlein et al., 2004). It was not developed as tool to be used outside clinical trials. The goal was to choose tests that took less than 15 min to complete and that the total time to complete the battery would not exceed 90 min. Additionally, the tests must be reliable and valid and be associated with functional outcome (Nuechterlein et al., 2008).

Prior to creating the MCCB, schizophrenia research often did not use instruments standardised for measuring cognitive performance in schizophrenia, but instead used neuropsychological tests or test batteries based on their respective range of use for the targeted domains in question (Buchanan et al., 2011; Heinrichs & Zakzanis, 1998). The prospect of the MCCB battery was aimed at forming a consensus of cognitive function in schizophrenia, as well as developing a "gold standard" for standardized examination of cognitive function in schizophrenia (Buchanan et al., 2011; Glahn et al., 2007; Green & Harvey, 2014; Green, Nuechterlein, et al., 2004; Nuechterlein et al., 2008; Rund et al., 2013). Kern et al. (2008) sought to identify the relevant cognitive domains in schizophrenia based on consensus of 68 experts that reviewed extensive research of more than 90 neuropsychological tests (Green et al., 2014; Kern et al., 2008). The aim was to establish an accepted standard for measuring the cognitive change in schizophrenia derived from a factor-analytical approach (Nuechterlein et al., 2008).

Six main cognitive domains were initially recommended for inclusion in the MATRICS-NIMH consensus cognitive battery (MCCB): *Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning and Memory, Visual Learning and Memory,* as well as *Reasoning and Problem-solving*. After a thorough debate, a seventh domain *Social Cognition* was also included, as it was thought to be an ecologically important domain, and to be a mediator between other domains and functional outcomes (Green et al., 2014; Nuechterlein et al., 2008). The six selection criteria for inclusion in the MCCB were test-retest reliability, practice effects, practicality, tolerability, and relationship to functional outcome (Nuechterlein et al., 2008).

Further, the co-norming of MCCB entailed the administration of the test battery on 300 individuals (stratified by age, gender, and educational level) included from five different sites and standardisation of the different tests used on the same norm group, which made it possible to conduct a profile of performance across different domains and examine the relationships among scores of different tests. In the commentary by Green et al. (2014) that followed, the results from several multisite clinical trial study the MCCB were evaluated in terms of test quality, sensitivity to treatment effects, and covariation in biomarkers (Green et al., 2014). They concluded that the MCCB was a feasible and fair method for assessing change in cognition in schizophrenia, and that it demonstrates good psychometrics with sensitivity to improvements following clinical trials. This was supported in later studies of the latent structure of cognition by confirmatory factor analysis and psychometric characteristics of schizophrenia (Georgiades et al., 2017; McCleery et al., 2015).

1.3.1 The Norwegian standardisation of MCCB

Rund et al. (2010) were the first researchers in Norway to translate and apply the use of MCCB in the Norwegian population within the Research Unit of Neuropsychopathology (RUN) at the University of Oslo (Rund et al., 2010). The Norwegian standardisation project aimed to determine the applicability of the American norms to a non-English-speaking population (Rund et al., 2013). They used the same norms; 300 people, stratified by gender, educational level, and age between 16 and 69. The sample was included from high schools in the Oslo area and by advertising. Their results showed applicability also in the Norwegian sample with discrepancies within 1 Standard deviation (SD) from the American norms and minor gender effects in favour of women speculated to arise from an expanded age span (Rund et al., 2013). Interestingly, they found some age-related differences, showing significantly better visual learning performance in the elderly group, and better verbal learning in the younger group, which differed from the American norms. Differences in educational level were interpreted to be of cultural origin due to differences in mandatory education in the US and Norway. The Norwegian translation of MCCB was done in collaboration with Kern et al. (2008) and approved by the National Institute of Mental Health (NIHM). A recent factorial analysis of the MCCB, the theoretical domain structure of the MCCB was recently tested (Mohn et al., 2017). Results showed that the theoretical domain structure could not be demonstrated in the Norwegian sample, and concluded that the MCCB generates the same cognitive domains through factor analysis in both Norway and the USA,

but different from the suggested by the MATRICS project (Mohn et al., 2017). However, the MCCB is commonly used in Norway now in schizophrenia research. The first study used MCCB on a Norwegian population with a healthy control group to investigate a neuropsychological profile in schizophrenia patients with Early-Onset of psychosis (EO). Except for social cognition, schizophrenia participants performed significantly lower than the healthy control group in all domains (Holmén et al., 2010). Smelror et al. (2019) have conducted a multi-site study standardisation study of the applicability of MCCB in Ireland, Norway, Sweden, and the United States, using the test performances of healthy youths (aged 12-19 yrs.) to develop an accessible and standardised dataset also for people below the age of 20 (Smelror et al., 2019).

1.3.2 HVLT-R & BVMT-R

The Hopkins Verbal Learning Test- Revised (HVLT-R) (Benedict et al., 1998) and the Brief Visuospatial Memory Test-Revised (BVMT-R) (Benedict et al., 1996) met the selection criteria for MCCB and both had six alternative forms. The HVLT-R and BVMT-R are both compatible psychometric tests for measuring learning and memory in the auditory/verbal and visuospatial domains, respectively (Nuechterlein et al., 2008).

The HVLT is a brief verbal learning and memory test with six alternate forms, which was revised to HVLT-R. This version includes a delayed recall trial and delays the yes/no recognition trial (Benedict et al., 1998). HVLT-R measures immediate recall and episodic memory and is administrated by reading a 12-item word list with a 2-second interval. After the final word is read off the list, the patient is asked to recall as many items as possible in any order. Two subsequential trials are administered in the same way. A delayed recall trial follows a 20–25-min interval in addition to a forced recognition trial filled with unrelated tasks and is a list of 24 words, including the 12 target words and 12 nontarget words. Traditionally, HVLT-R measures verbal learning using the total number of words recalled over the three trials given as a raw sum score. T-scores are also provided (Benedict et al., 1998).

The original edition of BVMT (Benedict & Groninger, 1995) had a limited range of recalls, it did not include a measure of learning over trials or recognition of the previously presented stimuli, and it was thought to be highly susceptible to fluctuations in inattention (Benedict et al., 1996). The limitation of its clinical use was questioned, which allowed for revision. Hence the improved test BVMT-R, which underwent a standardisation study by

Benedict and colleagues, proved to be a reliable and valid test of visuospatial learning with a reasonable degree of specificity (Benedict et al., 1996). The BVMT-R measures visual learning, in which the test person will be shown six figures in three trials of 10 seconds each and asked to draw them for each trial (Benedict et al., 1996). The performance is scored for the accuracy of their replication of the figures, and traditionally BVMT-R measures verbal learning using the total score over the three trials given as a raw sum score. T-scores are also provided. The BMVT-R measures immediate recall, learning, percentage retained, recognition discrimination index and recognition (Benedict & Groninger, 1995; Benedict et al., 1996).

1.5 Learning measures

1.5.1 Traditional learning measures: Learning curve and raw learning score

Learning curve (LC) and learning slope are alternate terms used in the literature and are both considered as a measure of learning over the course trials, often calculated in sum scores or T-scores. In this thesis, the LC is referred to as the differences in raw scores in trial 1-3. Gradual learning is traditionally investigated with LC. Horan et al. (2008) investigated impaired implicit learning in schizophrenia and found gradual learning through trial by trial and different learning curves between schizophrenia and healthy controls (Horan et al., 2008).

Another traditional method of calculating learning slope involves a difference score between the last trial and first trial, which is referred to as raw learning score (RLS) (Hammers, Duff, et al., 2021). When using HVLT-R and BVMT-R, the use of only the raw learning scores (RLS), is alternately defined by the differences between the third and first learning trials (Bonner-Jackson et al., 2015; Cirillo & Seidman, 2003; Egloff et al., 2018), or between the first and best trial of the trials T2 and T3 (Benedict et al., 1996; Hammers, Duff, et al., 2021).

In the current study, both HVLT-R and BVMT-R will be investigated using raw scores from trials 1-3 to analyse the LC. However, this method does not account for initial first trial performance, and therefore has significant limitations that stem from how these scores are computed. It can produce a ceiling effect that penalizes efficient first learners (Lynham et al., 2018; Spencer et al. 2022). Nevertheless, computed RLS scores of both HVLT-R and BVMT-R, using the third trial score minus the first trial score, will be investigated for exploration of different measures of learning. In this thesis, the LC and RLS will be investigated, respectively.

1.5.2 Novel learning performance measure: Learning ratio

Learning ratio (LR) is a novel method of measuring learning slope recently, to reduce inherent competition between the first and subsequential trial in traditional learning slopes (Spencer et al., 2022). The LR is proposed as an alternative method of calculating learning score that accounts for initial learning performance (Spencer et al., 2022). In several studies across different clinical samples using the HVLT-R and the BVMT-R, among other tests, the LR have been used for comparison of psychometric and predictive properties of learning (Hammers, Duff, et al., 2021; Hammers, Gradwohl, et al., 2021; Hammers, Spencer, et al., 2022; Hammers, Suhrie, Dixon, Gradwohl, Archibald, et al., 2022; Hammers, Suhrie, Dixon, Gradwohl, Duff, et al., 2022; Spencer et al., 2022). This novel learning slope measure was recently validated in a clinical population with Alzheimer's disease (AD) continuum disorders, using HVLT-R and BVMT-T (Hammers, Suhrie, Dixon, Gradwohl, Duff, et al., 2022).

The LR accounts for the first performance by retracting it from “the maximum amount that could have been learned”, while the RLS and LC use first performance as an indicator for “already learned material”. This way, with the LR, a performance can is viewed in relation to “what can be learned”, rather than only focusing on “what was learned”. LR is essentially represented by the number of items learned after the first trial, divided by the number of items “yet to be learned” (Spencer et al., 2022). The items “yet to be learned” is a formula in the denominator of the LR formula, with a calculation of the maximum of what you could have learned minus what was learned in first trial, which translates to “yet to be learned” or not yet learned. This is different from the traditional measures of LC and RLS, as this accounts for the capacity of what can be learned, rather than measuring insufficient learning in comparison with time or others. The formula of calculation of the LR will be presented and further elaborated on in the methods section of the thesis. Hammers, Duff, et al. (2021) found that the novel LR captures learning capacity better than traditional learning calculations, when taking into consideration the information learned at the first trial (Hammers, Duff, et al., 2021; Hammers, Suhrie, Dixon, Gradwohl, Duff, et al., 2022). The results of using LR shows a measurable capacity within a score usually ranging from 0.0 to 1.0. It is then usually multiplied by 100 to calculate “capacity used” in percentage (Spencer et al., 2022). This novel measure is more sensitive to individual variations (Hammers, Duff, et al., 2021).

1.6 Aims and hypotheses

In the current thesis, differences in verbal and visual learning and different types of learning curves in HVLT and BVMT between patients with schizophrenia and healthy controls is investigated. From the presented schizophrenia research, we know that verbal functioning is impaired and impacts performance in verbal learning and verbal memory tasks. Although less investigated, visual learning and memory are also found to be impaired in schizophrenia. Learning is traditionally measured using learning slopes or sum score performance measures, such as the RLS. With novel learning measures, such as LR, group differences in learning capacity in verbal and visual learning will be investigated. This thesis seeks to overall demonstrate usefulness of using LR as a method to improve learning score calculations, and to enhance the clinical utility of learning measures in schizophrenia.
The aims of the study are:

1. Investigate differences in verbal and visual learning performance in HVLT-R and BVMT-R in patients with schizophrenia and healthy controls.
2. Investigate group inter- and intra-variability in learning performances in HVLT and BVMT patients with schizophrenia and healthy controls, using the traditional measures of learning, the LC and RLS.
3. Investigate group inter- and intra-variability in learning performances in HVLT and BVMT in patients with schizophrenia and healthy controls, using the novel measures of learning LR and aggregated R.

Based on present and previous research, the following hypotheses will be considered when analysing the results:

1. Patients with schizophrenia will perform inferior to healthy controls in both verbal (HVLT-R) and visual learning (BVMT-R), when using the traditional measures LC and RLS.
2. Patients with schizophrenia will perform inferior to healthy in both verbal (HVLT-R) and visual learning (BVMT-R), when using the novel measures LR and aggregated R.
3. The novel measures of learning LR and aggregated LR will outperform traditional measures in detecting group differences and the sensitivity of measuring learning.

2. Methods

2.1 The thematically organized psychosis study

Data for the current thesis were collected as part of the Thematically Organized Psychosis (TOP) study at the Norwegian Centre for Mental Disorders Research (NORMENT). The TOP study is an ongoing prospective study aiming to increase insights into causes, trajectories, consequences, and new treatments for severe mental disorders.

2.1.2 Participants

Patients have been consecutively recruited in the TOP study from both in- and outpatient clinics in the south-eastern health region of Norway since 2002, predominately from the four major psychiatric hospitals in the Oslo region. Healthy controls from the same catchment areas were randomly drawn from the national statistics registry, invited to participate by letter, and screened over the telephone before inclusion.

General inclusion criteria: 1) age between 18 and 65 years, 2) having an IQ $\geq$ 70 3) speaking a Scandinavian language and having most of their compulsory schooling in Norway. In addition, for the schizophrenia group, they were required to have a diagnosis within the spectrum of psychotic disorders (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, bipolar and major depressive disorders with psychotic symptoms, or psychosis not otherwise specified).

General exclusion criteria: 1) history of clinically significant head injury 2) presence of a neurological or medical illness interfering with brain function. For the healthy control group, additional exclusion criteria were having a history of severe mental illness or first-degree relatives (parents or siblings) with a history of severe mental illness and substance abuse the last 12 months.

All participants receive an information- and consent form with a complete description of the study, the use of data, and the prospects of being invited to participate again later. They were informed that they could withdraw from the study and withdraw their consent at any given time. All participants were offered compensation of 500 NOK for their participation. The current study included 179 with schizophrenia spectrum disorder and 658 Healthy controls who had completed both HVLT-R and BVMT-R and fulfilled inclusion criteria.

2.1.3 Demographics

For group comparisons, independent sample t-tests were conducted to investigate differences between groups in age, IQ, and education. Chi-square tests were conducted to examine group differences between group affiliation, gender, and hand, using Pearson's Chi-square 2-sided significance as this measure looks for general coherence between two categorical variables.

Table 1

Demographic and clinical characteristics of the sample

	Patient (n = 179)	**Control (n = 658)**	**Group comparisons (2-sided p)**
Age	28.55 (9.1)	33.63 (9.2)	<.001*
Gender (male/female)	108 (60.3%) / 71 (39.7%)	358 (54.4%) / 358 (54.4%)	.175
IQ (WASI)	101.79 (13.4) [a]	114.77 (10.3)	<.001*
Education (years)	12.76 (2.4) [b]	14.70 (10.3)	<.001*
Hand [c]	Right = 160 (89.4%) Left =15 (8.4%) -	Right = 577 (87.7%) Left = 75 (11.4%) Ambidextrous 3 (0.5%)	.337
AAO [d]	24.1 (8.2)		
DOI (years) [d]	4.5 (5.9)		
GAF-S	48.9 (12.7)		
GAF-F	48.5 (12.5)		
PANSS total	59.1 (12.7)		
Positive	8.7 (3.9)		
Negative	13.4 (5.6)		
Disorganized	5.6 (2.5)		
Excited	5.3 (1.8)		
Depressed	7.4 (2.8)		

Note. Continuous variables reported as mean (SD). Categorial variables are reported as frequency (percentage). * p<.001, **p<.01, ***p<.05. IQ (WASI) = Wechsler Abbreviated Scale of Intelligence. [a] 1 missing, [b] 2 missing, [c] missing 4 patients / 3 controls, [d] 4 missing. WAAO = Age at Onset of psychosis, DOI = Duration of Illness (years), GAF = Global Assessment of Functioning, PANSS = Positive and Negative Syndrome Scale, GAF-S = Global Assessment of Functioning symptoms, GAF-F = Global Assessment of Functioning function. Continuous variables are reported as mean (SD).

The independent sample t-tests show significant differences between the groups in terms of age, IQ, and education. Differences reflect higher age, education, and IQ in the control group, compared to the patient group. There are no significant differences in gender between groups.

2.2 Measures

2.2.1 Clinical measures

Clinical assessment and interviews of the patients were conducted by a trained clinical psychologist or medical doctors, using a comprehensive clinical and neuropsychological protocol. Healthy controls were not assessed using clinical instruments. For this study, a few selected clinical measures will be used to describe the demographics of the schizophrenia patient group.

The Structural Clinical Interview for DSM-IV Axis-I disorders (SCID-I, Module A-E) (Spitzer et al., 1992) was used for diagnostic evaluations of the patients, only conducted by trained medical professionals.

The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to assess symptom presence and severity for schizophrenia spectrum disorders. The scale consists of 30 items in total, divided into three symptom subdomains of positive symptoms (7 items), negative symptoms (7 items) and general psychopathology (16 items). Each item is rated by severity from absent (1) to extreme (7), which allows a calculation of total scores and subscale scores. Factorial scale analysis has challenged this conventional three-factor model in recent years (Langeveld et al., 2013; Pinna et al., 2014; Wallwork et al., 2012) (Wallwork, Hashimoto, Weinberger & Dickinson, 2012; Langeveld et al., 2013; Pinna, Bosia, Cavallaro& Carpiniello, 2014). Consequently, a more differentiated five-factor structure of Positive, Disorganized, Negative, Excited, and Depressive symptoms have been established and utilised as a consensus five-structure model for use in psychotic disorders recommended by Norwegian health authorities. The scale was administered in a semi-structured interview (SCI-PANSS) which takes 30-45 to complete.

The Global Assessment of Functioning scale (GAF; APA, 1987) was used in the patient group to assess the level of functioning and state of mental illness severity.

2.2.2 Cognitive measures

Cognitive assessments were performed by clinical psychologists while trained psychology psychologist students assessed the control sample. All assessors were trained and calibrated on the measures and supervised by a neuropsychologist and senior researcher. The test battery consisted of tests measuring functions known to be affected in schizophrenia patients and consisted of measures of intelligence and the MCCB. For the current study following tests were included.

For measures of intelligence, the Norwegian version of the Wechsler Abbreviated Scale of Intelligence (WASI) was used to estimate participants' IQ, using two subtests (*Matrix Reasoning* and *Vocabulary*). Scores in the Norwegian sample do not differ significantly from the original American sample (Siqveland et al., 2014). For this study, IQ will be used in several interaction analyses as a secondary factor.

For measuring verbal and visual learning, the HVLT-R and BVMT-R tests were administered as part of the MCCB with the Norwegian translation of the MCCB (Mohn et al., 2012). Participants were given thorough test instructions. Performance data recorded on both tests followed the MCCB manualised instructions previously described, deriving both raw trial scores, raw sum scores and sum score T-scores. The data is colloquially referred to as performance throughout this study and entails using only raw trial scores, raw sum scores and computed novel measures derived from raw scores.

2.3 Interrater reliability

All interviewers completed a SCID-I training program to conduct diagnostic evaluations with DSM-IV and had regular supervision by experienced clinical psychologists or psychiatrists. PANSS demonstrates high inter-rater reliability (Kay et al., 1988). The Norwegian version of the WASI demonstrates good inter-rater reliability (Brager-Larsen et al., 2001), as do the HVLT-R and BVMT-R (Burton et al., 2013).

2.4 Statistical analyses

Analyses were conducted using IBM SPSS 28. A descriptive analysis of the groups and clinical characteristics of the patient sample was conducted to display the demographic

characteristics of the sample of this study. Independent sample t-tests and a Chi-square test were conducted to compare continuous and categorical variables, with groups as fixed variables.

A general linear model (GLM) repeated measures ANOVA analysis was conducted to investigate the LC in HVLT and BVMT for both healthy controls healthy controls and schizophrenia patients. Further, independent sample T-tests were conducted to investigate learning measures from computed traditional RLS scores and computed novel LR measures in group comparison of schizophrenia patients and healthy controls.

For this analysis, measures of LC were calculated and computed as Raw Learning Score (RLS) and Learning Ratio (LR) for each of the HVLT and BVMT tests, as well as an aggregated score for both RLS and LR, using the formulas from Hammers et al. (2021). Effects were reported as partial eta squared.

$$\boldsymbol{RLS} = (\text{Final Trial} - \text{First Trial})$$

$$\boldsymbol{LR} = \frac{(RLS)}{(\text{Maximum Score per Trial} - \text{First Trial})}$$

$$\boldsymbol{Aggregated\ RLS} = (RLS\ \text{HVLT} + RLS\ \text{BVMT})$$

$$\boldsymbol{Aggregated\ LR} = \frac{(RLS\ \text{HVLT} + RLS\ \text{BVMT})}{(\text{Maximum Score per Trial from both tests} - \text{First Trial from both tests})}$$

Lastly, a Multivariate ANOVA was conducted to control for effects from demographics. Effect sizes are reported as Cohen's d, with a confidence interval of 95%, and significance is interpreted with an alpha level for all tests of 0.01. Some results are evaluated with an alpha level of .05.

1.6.1 Ethical considerations

As his study will use data from the TOP study at NORMENT, no separate application to REK (Regional ethics committee) was needed. The TOP-study has been approved by the Regional Committee for Medical and Health Research Ethics and the Norwegian Data Inspectorate. Ethical considerations must nevertheless be considered. The groups under study

are vulnerable to societal and clinical stigmatisation, and this thesis will strive to refer to them in a respectful and non-stigmatizing way.

TSD (Services for Sensitive Data) facilities, developed and operated by the IT-Department (USIT) at the University of Oslo, was used for storage and analysis of data. The data were anonymised when received. A computer with encrypted access to the NORMENT database will be used. The data file will be deleted from the NORMENT database on TSD when this study is completed.

3. Results

3.1 Descriptive statistics and group comparisons between demographic variables

The Independent Sample T-tests comparing groups to investigate differences/variance between groups for each continuous variable showed significant differences between schizophrenia patients and healthy controls in age, education, and IQ. The t-tests also showed equal variance for the IQ Measures within groups, with standard deviation showing more significant IQ variance within the healthy control group. This means that the groups differ demographically, as shown in Table 1. The Chi-square test investigated differences/variance between groups for each categorical variable, which showed no significant differences between schizophrenia patients and healthy controls in gender or handedness.

3.2 Learning curve: GLM repeated measures ANOVA

A GLM repeated measures ANOVA was conducted to investigate the LC of both schizophrenia patients and healthy controls, in both HVLT-R and BVMT-R, with a Bonferroni adjustment of the confidence interval. With GLM repeated measures ANOVA, it is possible to investigate the LC from trial 1, to trial 2, to trial 3, using raw performance scores from each trial in each of HVLT-R and BVMT-R. The raw HVLT-R trial scores indicated the number of obtained words remembered from the list of 12 words repeated in three trials. The mean raw score was then calculated for patients and healthy controls and used to compare groups per trial. The raw BVMT-R trial scores indicated the number of points given for correctly reproduced figures shown for 10 seconds, repeated in three trials.

The mean raw score was then calculated for patients and healthy controls and used to compare groups per trial. Table 2 also shows how learning measures from trial 1 to trial 3 controlled for covariates were significantly affected by group affiliation and significantly by all continuous variables (age, education, and IQ).

Table 2

Learning Curve (LC) between groups

Performance measures	Age	IQ (WASI)	Education (years)	Group comparisons
HVLT-R				
Sig.	.432	<.001*	<.001*	<.001*
η_p^2	.001	.100	.016	.048
HVLT-R T1				
Sig.	.745	<.001*	.011	<.001*
η_p^2	.000	.087	.008	.015
HVLT-R T2				
Sig.	.600	<.001*	.003	<.001*
η_p^2	.000	.075	.011	.047
HVLT-R T3				
Sig.	.049	<.001*	<.001*	<.001*
η_p^2	.005	.052	.018	.049
BVMT-R				
Sig.	<.001*	<.001*	.210	<.001*
η_p^2	.096	.113	.002	.082
BVMT-R T1				
Sig.	<.001*	<.001*	.504	<.001*
η_p^2	.066	.099	.001	.037
BVMT-R T2				
Sig.	<.001*	<.001*	.084	<.001*
η_p^2	.079	.076	.004	.074
BVMT-R T3				
Sig.	<.001*	<.001*	.385	<.001*
η_p^2	.078	.083	.001	.089

Note. η^2 = Partially Eta Squared. * p<.001

Included: 179 schizophrenia patients and 655 healthy controls.

As depicted in Table 2, the GLM repeated measures ANOVA analysis showed significant differences in the LC between the groups, with no overlap between confidence intervals and concerning covariance intervals from age, education, and IQ. Group affiliation to schizophrenia patients shows an overall significant effect on learning in a trial. This supports the hypothesis of the group affiliation effect and is in line with first aim of this thesis. The age effect in BVMT-R trial scores is also in line with the initial findings of Nuechterlein et al. (2008). In both HVLT-R and BVMT-R, IQ shows a significant difference

between group in trial scores timepoints, which means at IQ influences separate trial scores. One would then expect differences in effect of education on trial scores as well, as education often is considered associated with IQ, but education only shows a significant interaction effect on learning on HVLT-R T3 and overall performance on HVLT-R. Gender effects were initially found in the standardisation of the original MCCB battery. However, in the Norwegian standardisation of MCCB, the gender effect was not the same, suggesting a broader sample of the Norwegian population (Mohn, Sundet & Rund, 2013). This might also be the case in the current study, as no gender effects on trial scores was found in neither of the three trials of HVLT-R and BVMT-R.

As shown in Table 3, The GLM repeated measures ANOVA also showed that there is a significant change in trial score (means) over time, Wilks' $\lambda = 0.90$, F (2, 828) = 45.48, $p <$ .001, partial eta squared = .10, which effectively means that both schizophrenia patients and healthy controls experience learning effect, in both HVLT-R and BVMT-R.

Table 3

Learning Curve (LC) over time

Parameter	Measure	Lower Bound	
		Sig.	η_p^2
Trials	HVLT	<.001*	.056
	BVMT	<.001*	.056
Trials * Age	HVLT	.114	.003
	BVMT	.134	.003
Trials * IQ	HVLT	.011***	.008
	BVMT	.003**	.011
Trials * Education	HVLT	.564	.000
	BVMT	.366	.001
Trials * Group	HVLT	.036***	.005
	BVMT	.169	.002

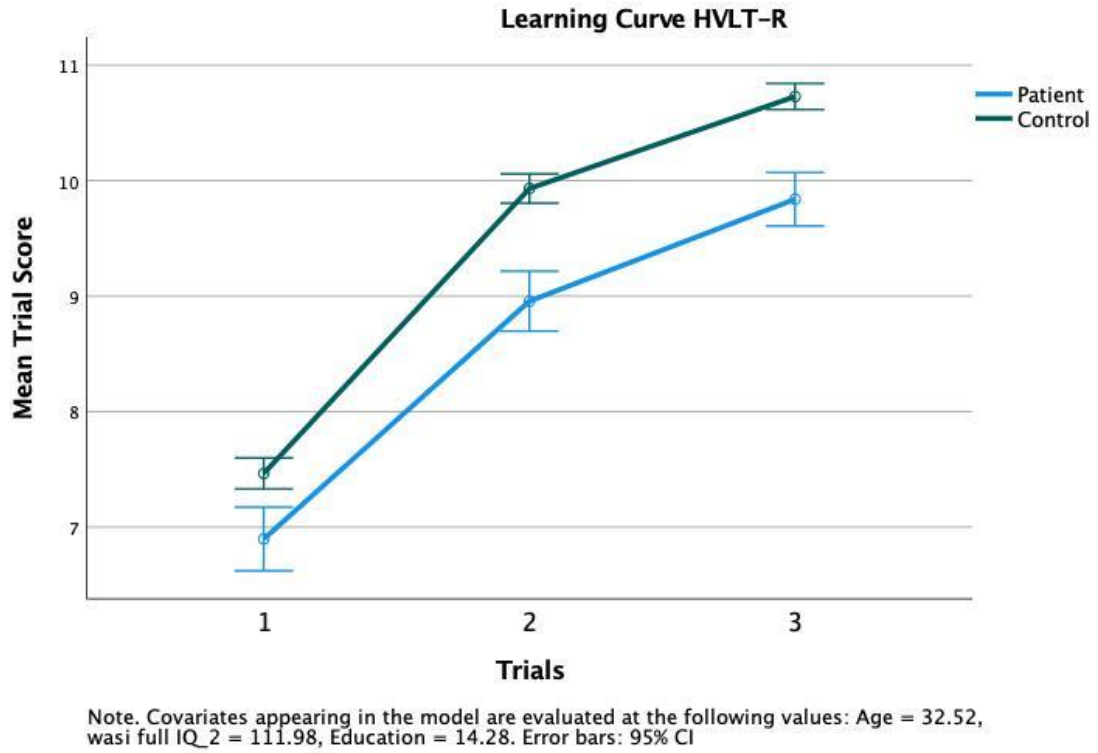
Note. η_p^2 = Partially Eta Squared * p<.001, **p<.01, ***p<.05.
Included: 179 schizophrenia patients and 655 healthy controls.

This is also visualised in figure 1 and figure 2, accounting the covariates. Further, the significant cross-effect between time and IQ, was strongest in BVMT-R and only slightly significant in HVLT-R when widening the threshold to p<.05. This means that IQ potentially

influences how people learn over time. And again, the effect of education did not show any significance of learning over time. In Mauchly's test of sphericity, both HVLT-R and BVMT-R results were significant, which means the Lower Bound of significance was chosen. Overall, when the LC was used for depicting a measure of learning over time, the results of the current study show that schizophrenia patients perform inferior to healthy controls, in learning trial by trial, in both verbal and visual learning.

Figure 1

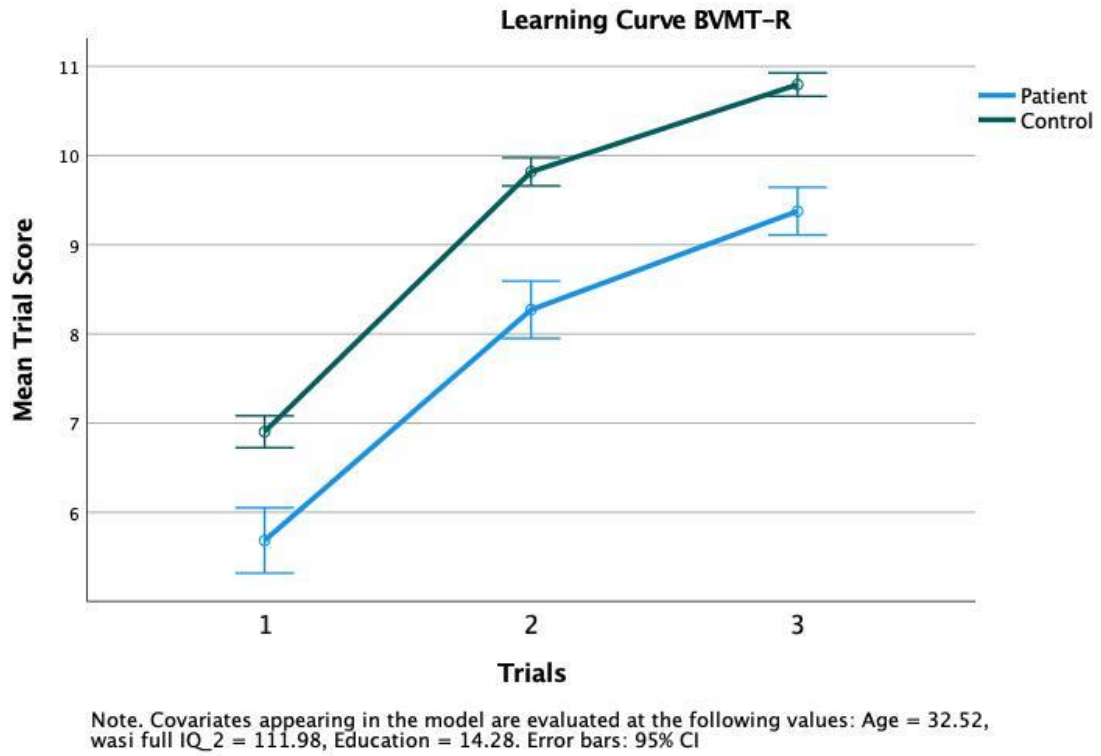
Mean Trial score between groups and across trials for HVLT



Note. Covariates appearing in the model are evaluated at the following values: Age = 32.52, wasi full IQ_2 = 111.98, Education = 14.28. Error bars: 95% CI

Figure 2

Mean Trial score between groups and across trials for BVMT



3.3 RLS, LR and aggregated scores: Independent samples T-tests

The independent samples T-tests comparing the RLS and LR scores of both HVLT and BVMT performance was conducted to investigate and compare effects sizes between traditional and novel learning measures. The results showed no significant differences between healthy controls and schizophrenia patients in HVLT-RLS or BVMT-RLS scores, nor the aggregated-RLS scores. Interestingly, the results showed significant differences between the groups with large effect sizes in both LR of HVLT-R, BVMT-R LR and aggregated LR HVLT-R/BVMT-R, as shown in Table 4. IN the two-sided comparison, a difference within groups is also present in those three measures.

There were significant differences in HVLT-LR scores between healthy controls (*M* = 0.7, *SD* = 0.3) and schizophrenia patients (*M* = 0,5, *SD* = 0.3; *t* (824) = -6.9, *p* = <.001, two-tailed). The magnitude of the differences in the means (mean difference = -.17, 95% confidence interval [-.22, -.12]) was medium (Cohen's *d* = .6).

Significant differences were also found in BVMT-LR scores between healthy controls (*M* = 0.8, *SD* = *0.3*) and schizophrenia patients (*M* = 0.6, *SD* =0.3; *t* (269) = -8,0, *p* = <.001, two-

tailed). The magnitude of the differences in the means (mean difference = -.21, 95% confidence interval [-.26, -.16]) was large (Cohen's *d* = .7).

Also, the results showed significant differences in aggregated-LR scores between healthy controls (*M* = 0.8, *SD* = 0.8) and schizophrenia patients (*M* = 0.6, *SD* = 0.2; *t* (269) = -8,0, *p* = <.001, two-tailed). The magnitude of the differences in the means (mean difference = -.39, 95% confidence interval [-.46, -.30]) was large (Cohen's *d* = .8).

It is worth mentioning that performances with no difference between trials are penalized with the LR, as they mathematically fall out of the metric and leaves a reduced number of included participants. This is especially evident in BVMT-R LR, with 2 schizophrenia patients and 20 healthy controls are left out of this analysis, but also is the case for healthy controls HVLT-R LR.

Table 4

Comparison of raw learning scores (RLS) and learning ratio (LR) measures

Variable	Patient	Control	Group comparison (2-sided p)	Cohen's *d*
HVLT-R RLS	179, 3.2 (1.7)	658, 3.2 (2.1)	.735	.028
BVMT-R RLS	179, 3.9 (2.1)	658, 3.8 (2.1)	.715	.031
HVLT-R LR	179, 0.5 (0.3)	647, 0.7 (0.3)	<.001*	.583
BVMT-R LR	177, 0.6 (0.3)	638, 0.8 (0.3)	<.001*	.703
Aggregated RLS (HVLT-R+BVMT-R)	179, 7.0 (2.8)	658, 7.0 (2.8)	.952	.005
Aggregated LR (HVLT-R+BVMT-R)	179, 0.6 (0.2)	658, 0.8 (0.2)	<.001*	.848

Note. All values of learning measures are *n, Mean (SD)* unless listed otherwise. * p<.001, **p<.01, ***p<.05.

As hypothesised, the novel measures LR and aggregated LR outperformed traditional RLS measures in detecting significant differences in in learning between schizophrenia patients and healthy controls, in both HVLT-R and BVMT-R.

3.4 Controlling for effects: Multivariate ANOVA

From the initial descriptive analyses, the demographic variables such as age, IQ and education did show significant variance in, and difference between, groups, which could affect the effect sizes found in the independent sample t-tests. A multivariate ANOVA was conducted to control for this, with the results from this shown in Table 5.

Table 5

Controlling effects of learning measures (MANOVA/ANCOVA)

	Age	IQ (WASI)	Education (years)	[Patient]
HVLT-R RLS				
Sig.	.019***	.010**	.216	.042***
η_p^2	.022	.030	.000	.042
BVMT-R RLS				
Sig.	.304	.008**	.962	.237
η_p^2	.003	.019	.014	.016
HVLT-R LR				
Sig.	.155	<.001*	<.001*	<.001*
η_p^2	.007	.008	.002	.005
BVMT-R LR				
Sig.	<.001*	<.001*	.779	<.001*
η_p^2	.001	.009	.000	.002
Aggregated RLS (HVLT-R+BVMT-R)				
Sig.	.472	<.001*	.457	.031**
η_p^2	.016	.027	.003	.045
Aggregated LR (HVLT-R+BVMT-R)				
Sig.	<.001*	<.001*	.098	<.001*
η_p^2	.001	.016	.001	.006

Note. Learning measures as dependent and continuous variables as parameters. η_p^2 = Partial Eta Squared. * p<.001, **p<.01, *p<.05.
Included: 177 schizophrenia patients and 624 HEALTHY CONTROLS.

A Multivariate ANOVA was conducted with a confidence interval adjustment of Bonferroni and testing for homogeneity, to control for effects sizes initially found from age, education, and IQ.

As evident from the previous independent T-tests, performance with no change in trial performance are excluded from this analysis, leaving 177 schizophrenia patients and 624 healthy controls. The BVMT LR, HVLT LR, and aggregated LR measures were still significant with alpha levels of .001 and 0.05.
The results showed significant differences in RLS HVLT and aggregated RLS with an alpha level of 0.05, respectively, when controlled for effects of age, education, and IQ. To avoid redundancy of data, no descriptive matrices of means and interaction effects were presented of this.

4. Discussion

The current study sought to investigate verbal and visual learning performance in schizophrenia patients and healthy controls. Both traditional and novel measures of learning performance variability were computed and investigated, with leaning curves as conventional measures and learning ratios as novel measures. The results showed that schizophrenia patients performed inferior to healthy controls in all traditional and novel measures, with significant group differences in both HVLT-R LC and BVMT-R LC over the course of trials 1-3. The results also showed significant differences between traditional and novel measures within groups. Finally, when controlling for the effects of age, education, and IQ, the verbal and visual learning differences between schizophrenia patients and healthy controls were still significant. These findings will be discussed in terms of the respective measures.

4.1 Traditional learning measures

4.1.1 Learning curve (LC): Learning differences between groups and over time.

Previous research has shown that patients with schizophrenia perform inferior to healthy controls in verbal learning tests (Carrión et al., 2018; Flaaten, Melle, Bjella, et al., 2022; Fusar-Poli et al., 2012; Green et al., 2019; Heinrichs & Zakzanis, 1998; Nuechterlein et al., 2004; Toulopoulouand & Murray, 2004). The current results came to the same conclusion when using LC, with significant differences in performances in each trial between schizophrenia patients and healthy controls. With verbal memory being a predictor of functional outcome (Green et al., 2019), the significance of current results becomes important to reflect on different types of processes involved in verbal learning, when distinguishing between repeated performances in patients and healthy controls.

With research consistently showing markedly impaired performance across a wide range of cognitive tests and domains in schizophrenia, verbal learning deficits may be a part of complex impairment pattern. The deficient performance in each HVLT-R trial from using the LC may reflect different cognitive deficits in processing the verbal information, such as recall deficit, semantic encoding strategy deficit, auditory deficit, or even primary deficit in initial acquisition and encoding. Several studies have found these processes to be a factor in the verbal impairment of schizophrenia. The primary deficit in verbal learning have previously been found to be in the initial acquisition of information (Gold et al., 2000). Rather than an increase in forgetfulness or decay in memory, it seems that the initial processes of attaining verbal information is impaired in patients with schizophrenia, which could explain the current results of reduced learning performance in each trial.

Further, the encoding process of acquired information have been described as a rate-of-forgetting (Cirillo & Seidman, 2003; Toulopoulouand & Murray, 2004). However, as the immediate encoding is impaired in schizophrenia (Foley et al., 2008), semantic encoding strategy deficits develop verbal memory deficits when failing to semantically organize verbal information. This has proven a significantly strong predictor of verbal learning in schizophrenia (Hill et al., 2004), which implies that the semantic encoding strategy deficit seem unique to schizophrenia patients. Additionally, the encoding deficit in schizophrenia was explained by an additional perceptual deficit in auditory processing in the study of (Green et al., 2019). These involved processes in the verbal learning may potentially influence the current results in the LC of HVLT.

In line with previous research (Fett et al., 2020; Fu et al., 2018), the trajectory of the LC showed improvement for the patient group, but with a relative decline to the healthy controls. The LC also showed that the trajectory of LC in schizophrenia patients showed similar course, and thereby had the same effect, which means that the LC as a model show a learning effect in all participants. The LC therefore proved significant interaction effect with time, similarly to Hoff et al. (2005) and Fu et al. (2018). It is important to note that a relative decline in verbal ability is expected in schizophrenia, already in adolescence and prodromal phases (MacCabe et al., 2013). With this is mind, the LC assumably should sensitively detect significant differences between the patient group and heathy controls on all phases over the course of the illness. It has been suggested that the first trial can obscure perception the verbal learning ability (Spencer et al., 2022), which in turn could be explained by the immediate recall deficits. However, Gold et al. (1999) found that immediate recall improved in comparison to previous performances. This might explain trajectory of performances in the

LC, showing schizophrenia patients do obtain verbal learning, only in a compromised pace than healthy control. This is promising, considering the growing research stating patients with schizophrenia exhibit improvement in cognitive impairments, except for verbal memory (Carrión et al., 2018; Mesholam-Gately et al., 2009; Rodríguez-Sánchez et al., 2013; Rodríguez-Sánchez et al., 2008; Schaefer et al., 2013; Seidman et al., 2016; Torgalsbøen et al., 2015). Yet, the current results only showed improvement over trials, but never reached the level of healthy controls. As the verbal impairments precede onset of psychosis in schizophrenia (Fusar-Poli et al., 2012; Mohn-Haugen et al., 2022), and is stabile over the course if the disorder (Zanelli et al., 2019), the LC depicts a picture of a compromised verbal learning ability in schizophrenia. Some research suggests that these cognitive changes are only temporary and stabilises after the onset and over time (Fu et al., 2018).

As hypothesised, visual LC showed significant differences between patients and healthy controls in each of the BVMT-R trials, and visual memory impairments was therefore observed in people with schizophrenia, in line with previous research (Albus et al., 2002; Fusar-Poli et al., 2012; Green & Harvey, 2014; Mohn & Torgalsbøen, 2018). This may be due to a pattern of visual recall deficiencies, but patients have improved more than controls on a measure of immediate visual memory (Tracy et al., 2001). However, the group by time interaction was not significant for the BVMT-R performance, which means that the schizophrenia patients did not perform significantly different than healthy control over time in the BVMT-R. This could be attributed to a lesser immediate visual memory impairment, than verbal memory impairment (Hoff et al., 2005). Another explanation could be due to the heterogeneity of the groups, which means than different subgroups of cognitive impairment are present in the patient sample. From different studies we know that subgroups of cognitive impairment (Carruthers et al., 2019; Vaskinn et al., 2020) may affect the visual LC to a degree that strengthens the mean performance of the patient group. The current results may reflect the fact that time interacts with inherent intact ability within a sample, as subgroups of schizophrenia being relatively intact (36%) (Vaskinn et al., 2020), and around 30% of individuals with schizophrenia perform within the normal range of cognitive functioning (Fett et al., 2022). However, some studies also found reduced heterogeneity in visual learning after stabilisation of the disorder (Albus et al., 2019).

The slight effect of age in each of the BVMT-R trial performances, supports previous findings of Rund et al. (2013). Interestingly, they found significantly better visual learning performance in schizophrenia patients in the elderly group, but better verbal learning performance in the younger group. This age differences was not possible to investigate in the

current study, but would have been interesting to look at. Moreover, the LC found an effect of IQ over the course of trials in both verbal and visual learning. This is in accordance with a recent study who found that intellectual functioning (IQ) is lower in schizophrenia patients compared to healthy controls (Flaaten, Melle, Gardsjord, et al., 2022).

In another study, 70% of schizophrenia patients showed deterioration of IQ, following the onset of the disorder (Ohi et al., 2017). In an early review it was of pointed out that many patients may perform as much as 78% below the median of a healthy population, and below premorbid potential. They also stated that premorbid overall function is difficult to assess with IQ measures only (Heinrichs & Zakzanis, 1998). With this evidence in mind, IQ seems to be a potentially important confounder of influence on how people learn over time. But, when controlled for in the current study, the difference between schizophrenia patients and controls using LC was still significant.

4.1.3 Raw learning score (RLS): A simplified measure of learning between two time points

A significant difference in learning when using RLS was recently found between healthy controls and patient populations, with time considered as an effect and (Hammers, Suhrie, Dixon, Gradwohl, Duff, et al., 2022; Spencer et al., 2022). The current study did not produce such results.

A third of schizophrenia perform within normal range (Fett et al. 2022), this does not seem to be the case in the current study when looking to other current results from using different measures. At the same time, the standard deviations in verbal learning performance in the current results show a difference between patients and healthy controls. This could reflect a hidden impairment in accordance with the results of the LC, even if not significantly different to healthy controls, which would be in line with recent findings (Hammers, Suhrie, Dixon, Gradwohl, Duff, et al., 2022). When controlling for confounds, the RLS suddenly show a slight effect of IQ, as could be expected already established in the results of the LC, and from previous literature (Flaaten et al., 2022; Ohi et al., 2017). Hence, IQ may some degree be protective of impairment detection, when using the RLS.

Furthermore, in the current study the verbal RLS showed a slightly significant effect of age on verbal learning for all participants. This finding was also pointed out in the data from the HVLT-R, and BVMT-R manuals, indicating that RLS slightly declines with age (Nuechterlein et al., 2008).

The RLS measure is often used when investigating difference between cognitive affected and non-affected populations (Hammers, Duff, et al., 2021), and is essentially exploring learning in a simple and low-cost way. This makes a valid point in choice of the RLS, as it does not demand complicated analysis. Unfortunately, the RLS have significant limitations that stem from how these scores are computed (Spencer et al., 2022). When the RLS reflecting "no learning" ability, if no change in scores between trials, regardless if obtained high or low scores on both trials. The lack of group differences in verbal or visual learning in the current results might be due to this problem. The measures HVLT-R and BVMT-R was used in the current study to elucidate discrepancies between schizophrenia patients and healthy controls. But when only rewarded if change, the RLS abrogated the variance between groups and consequently proved less sensitive and may indicate false variance in heterogeneity.

RLS scores in individuals with minor cognitive illness and in controls have shown superiority, to performances of individuals with major neurocognitive illnesses, and those who performed exceptionally well on the tests (Hammers, Duff, et al., 2021; Spencer et al., 2022). Thus, the group difference between schizophrenia patients and healthy controls could subside, due to the ceiling effect that penalizes efficient first learners (Lynham et al., 2018; Spencer et al., 2022), which might have been the case in the current study. In sum, the RLS proved poor in to detecting variance between patients and healthy controls, and seems not good enough for understanding the capacity of learning, in line with previous research (Hammers, Gradwohl, et al., 2021; Spencer et al., 2022).

4.2 Novel learning performance measures

From the emerging studies, LR sensitively detects significant differences between patients and healthy controls using HVLT-R LR and BVMT-R LR, in populations with mild cognitive impairment (MCI) (Hammers, Duff, et al., 2021; Hammers, Gradwohl, et al., 2021; Hammers, Suhrie, Dixon, Gradwohl, Duff, et al., 2022). As Spencer el at. (2022) states, LR scores tend to show differences that are equivalent or of more significant disparity as RLS and differ according to age, gender, and clinical status. However, little is known regarding the variance of these scores (Spencer et al., 2022). In the following, the use of LR as a novel learning measure will be discussed, along with an elaboration of using aggregated scores. To the best of found knowledge, this is the first time the LR measure has been used in schizophrenia sample and population.

4.2.1 Learning Ratio (LR)

When applying the guidelines using the LR by Spencer et al. (2022 to the current results, the verbal LR of 0.5 in the patient group, can be translated into 50% learned of available verbal information over successive trials in schizophrenia patients, versus 70% in healthy controls. This means schizophrenia patients show a 20% gap in capacity for verbal material yet to be learned, different from healthy controls and thereby the expected premorbid function if healthy. The capacity deficit of 20%, might be compromised due to a global cognitive impairment, as impairment can be diffuse as it presents different across domains (McCleery & Nuechterlein, 2019). This can also reflect the magnitude of the measure. Learning impairment in schizophrenia is reflected in performances well below the control mean over time in HVLT-R performance (Cirillo & Seidman, 2003), with a generalised cognitive deficit of 1.5 SD below the control group's mean in both verbal and visual learning (Bilder et al., 2000). The current study found similar results with schizophrenia patients performing more than 1,5 SD below healthy controls. As evidenced in previous literature, this may reflect an expression of a developmental lag in schizophrenia patients (Melle, 2019; Mohn-Haugen et al., 2022), along with adverse cognitive deficits in in both attentional processes (Mohn & Torgalsbøen, 2018), and memory encoding (Cirillo & Seidman, 2003; Gold et al., 2000). With impairments in learning capacity as a developmental lag, patients with schizophrenia will become more significantly impaired after onset or later in life (Mohn-Haugen et al., 2022). Moreover, it might manifest in different areas in life early on, as social disability associated with the disorder (Green, 1996), and in vocational function (Falkum et al., 2017). Notably, clinical recovery in FEP after 1 year has been found (Simonsen et al., 2017), which makes the use of the LR interesting, for better understanding how learning capacity develops over time. Knowing that UHR differs especially in terms of magnitude in learning impairment (Carrión et al., 2018; Fusar-Poli et al., 2012), this seems effective as a measure of cognitive capacity in the delineation of the course of the illness. Curiously, changes in verbal learning have shown to be only temporary (Fu et al., 2018), which mean that for best depiction of learning capacity in schizophrenia it needs to be assessed over longer periods of time.

LR predict a learning ratio of the respective measure in verbal or visual learning. From previous studies, we know that verbal learning is impaired in both initial recall and learning rate in FEP patients (Egloff et al., 2018). In terms of the visual LR, the current result showed 60 % learned of available visual information over successive trials in schizophrenia patients versus 80% in healthy controls. This supports previously mentioned literature, emphasizing

verbal learning to be the most compromised cognitive domain of the to. Also, the standard deviations within groups are the same between schizophrenia patients and healthy controls, which show robust findings of impaired capacity in the patient group.

The relative capacity difference between visual and verbal learning in patients with schizophrenia is 10%, favouring visual learning. This attest to previous research finding relative improvement in FEP patients over a period of 10-year period (Hoff et al., 2015). Simultaneously, is also portrays deficient visual learning compared to healthy controls.

The greatest magnitude of effect sizes in the LR measure was in the visual LR. This may be a contrary interpretation to previous findings of the learning rate being more impaired in verbal learning, compared to healthy controls (Egloff et al., 2018). Yet, the groups in the current study might be more heterogeneric in visual learning abilities than in verbal learning abilities. Others suggest that such results could reflect compromised patterns of cognitive functioning prior to the onset of overt psychosis (Bang et al., 2015; Bortolato et al., 2015; Fusar-Poli et al., 2012; Green et al., 2019). Which mean that more cognitive functions than visual learning processes may be in play, affecting the verbal learning LR.

In the review of McCleery and Nuechterlein (2019) they established that impacts on impaired cognition are diffuse, as it can be found across many cognitive domains. Which means, the cognitive function related to verbal memory might be measured when investigating verbal learning (Heinrich & Zakzanis, 1998), and vice versa. As we know, the strongest evidence for impairment pre-onset was for verbal learning and memory, along with executive function, mental processing speed, and social cognition (Mohn-Haugen et al., 2022). Together, this outlines a complexity in the processes involved in the capacity to learn either verbal or visual material.

Due to the solid evidence of learning impairment in schizophrenia, and that generalized cognitive impairment is robust and over time (Schaefer et al., 2013), a suggestion of cognitive dysfunction as a potential marker for diagnosis and prognosis have been made (Catalan et al., 2021). The current results of verbal LR and visual LR scores support this, with robust findings in both verbal and visual leaning impairment. The strongest predictor of schizophrenia seems to be the relative decline in verbal ability present already in adolescence, preceding clinical symptoms (MacCabe et al., 2013). In concurrence with the current results, the LR seem to fit this prediction of a clinical sensitive reflection of capacity and an indicator of prodromal phase. The current findings of the LR are important in a recovery perspective, with respect to the possibility elucidating the learning capacity in individuals with schizophrenia. As previous research has established, 6.5% FES patients experienced reduction in clinically significant

impairment over a 10-year period (Flaaten et al., 2022). With verbal learning being among the most critical cognitive impairments predicting psychosis, and prognosis, a better understanding of the reduced capacity for learning seems informative for cognitive remedies. Hence, when allowing for an interpretation of the capacity to learn as compromised, the LR evidences a steeper drop in learning efficiency, than otherwise known in schizophrenia literature.

4.2.2 Aggregated scores

LR show promise as a learning measure. However, several psychometric issues must be addressed, such as normative expectations and information on performance variability, for LR to be a guiding psychometric measure of learning in schizophrenia. One way of doing this is by aggregation of scores, as pointed out by Spencer et al. (2022).

4.2.3 Aggregated LR

The aggregated LR has already proven valuable as a learning measure across clinical populations (Hammers, Duff, et al., 2021; Spencer et al., 2022). In the current results, the aggregated LR score had the strongest effect size as a measure of capacity to learn, and effectively shows solid differentiation between cognitive impaired and non-impaired individuals (Spencer et al., 2022). The utilisation of aggregated LR therefore seems important in the capture of prodromal symptoms, and the understanding of clinical presentation of schizophrenia pre-onset (Mohn-Haugen et al., 2022). The current results showed high level of confidence in significance between the patients and healthy controls, even after controlling for confounds. This is in line with recent research (Hammers, Suhrie, Dixon, Gradwohl, Archibald, et al., 2022; Hammers, Suhrie, Dixon, Gradwohl, Duff, et al., 2022). The small effect of IQ in the aggregated LR on all participants have not yet been found in the studies of validating demographically adjusted normative data for the LR, but an effect of age has been found (Hammers, Duff, et al., 2021; Hammers, Suhrie, Dixon, Gradwohl, Duff, et al., 2022).

With aggregated scores, schizophrenia patients show significantly different learning than healthy controls in the current study, and the aggregated LR has the overall largest effect size between all measures of RLS and LR. Concurrently, in the initial analyses showed some significant differences in demographics between groups, which could serve as confound on this large effect size. A multivariate ANOVA was conducted to address this, in line with

previous literature addressing potential confounds in schizophrenia (Cirillo & Seidman, 2003). Regardless, the LR upheld a medium effect size after controlling for confounds and showed significant differences in verbal and visual learning performance between groups.

The aggregation of LR scores also showed significant differences in overall learning capacity between schizophrenia patients and healthy controls. The aggregation thereby served as an amplification of the statistical strength of the learning measure in question, in line with previous studies (Hammers, Duff, et al., 2021; Spencer et al., 2022). Subsequently, this study provided unique means and standard deviations of schizophrenia patients different from healthy controls, using both single LR and aggregated LR scores. We know that patients with schizophrenia presents as a disorder with cortical patterns of deterioration in later phases of life (Foley et al., 2008), which makes this measure valuable for assessments of learning capacity in schizophrenia in later stages of life.

Some participants were automatically left out of the analysis of the LR scores due to performances without change between trials. For the same reason they became missing in the analyses of the current study, as they did not allow for calculation in the metric of LR. Hence, single missing words during HVLT-R may create low reliability. This same issue has been observed in the RLS score in the CVLT-II manual (Delis et al., 1987-2000). This can create a problem when clinically translating results of learning capacity, for instance in settings of cognitive remedy therapy and vocational training, as change in learning and therefor capacity to learn subsides.

4.2.4 Aggregated RLS

RLS discrepancies have been apparent between groups, but mainly only after being magnified when applying it into the formula of LR or using aggregated LR (Hammers, Duff, et al., 2021; Spencer et al., 2022). This was not the case in the current study. In contradiction previous research evidence of cognitive impairment, the aggregated RLS did not detect verbal or visual impairments in schizophrenia. Only after controlling for confounds within and between groups, aggregated RLS only gained slightly better significant strength with adjusted alpha level of 0.5.

4.3 Implications and future directions

This thesis supports and expands earlier findings of impairments in verbal and visual learning in schizophrenia, and also adds to the growing body of studies employing HVLT-R and BVMT-R as measure of learning impairments. In summary, the results of the LC and LR cohere with the hypothesis of this thesis. Overall, the use of LC, RLS and LR proves as measures of learning, albeit with different strengths and with different conclusion of the same sample. Further studies should seek to elaborate on the LR as a measure of learning. Additionally, investigating neurobiological substrates of the LR may add value to the use of the LR in informing diagnostic and prognosis of schizophrenia.

To the best of found knowledge it is not yet known to what extent differences in LR scores between schizophrenia and healthy reflects memory or learning deficits in schizophrenia, as this is the first study to investigate this. In the current study, the mean of verbal learning impairment was 50% and the mean of verbal learning impairment was 60% in schizophrenia patients. These results have resemblance to the work of Spencer et al. (2022). they had a cut score of 42.9% for LR, which had sensitivity of 80.7% and specificity of 75.7%, for detecting neurocognitive diagnosis (Spencer et al. 2022). If applying this knowledge and use of the LR to schizophrenia populations, perhaps this presents a possibility of adding value to diagnostic tools of pathologically differentiating schizophrenia patients from healthy controls.

In the future LR can be normed and investigated in corroboration with functional measures such as GAF. This could allow for the LR to better inform clinical decision-making and treatment, especially for cognitive remedy therapy and vocational training. Recent studies have calculated and validated normative comparisons for the LR and the Rey Auditory Verbal Learning Test (RAVLT), based on demographic characteristics of age, sex, and education, which now permit the LR -RAVLT to be used to inform clinical decision-making and treatment (Hammers, Spencer, et al., 2022). When considering the recent validation studies of the LR, it presumptively gives promising opportunity for replicating such a process for the schizophrenia population. To generate demographically corrected normative data, future replication studies of the work done by Spencer et al. (2022) could apply linear regression analyses for both the LR HVLT-R, the LR- BVMT, and Aggregated LR (HVLT-R/ BVMT-R) scores (Hammers, Duff, et al., 2021). Also, using a regression model to correlate the LR measures of different tests and with other measures, would be a good start towards developing norms for the LR in patients with schizophrenia populations.

Additionally, better understanding of learning capacity impairment could potentially aid the assessment of who will profit from cognitive remediation. Impaired learning capacity in schizophrenia may influence a range of other cognitive abilities along with occupational and community functioning, as well as educational and psychosocial difficulties. For instance, Bryson and Bell (2003) investigated verbal learning predictors of vocational development and learning rates in work related tasks. Verbal memory was important for sustained improvement directly impeded learning on the job. The findings of the current studies reflect similarities in learning ability in schizophrenia patients, but with distinctive learning outputs from the different learning measures. Another study stated verbal memory important for sustained occupational improvement and vocational rehabilitation (Lystad et al., 2016). These findings are important when considering the evidence of attainable competitive employment in schizophrenia, when using cognitive remediation in vocational rehabilitation (Skancke Gjerdalen et al., 2022). In advanced therapeutical settings, clinicians should incorporate the understanding of potential difficulties from reduced learning capacity to better facilitate successful learning. Such as, therapeutic settings with less verbal instructions to remember, or vocational training with less visual stimuli to navigate in, in work related tasks.

4.6 Strengths and Limitations

An apparent strength of this study is the inclusion of a healthy comparison group and the substantial number of participant (n = 837). This warrants satisfactory statistical power. The well-established, reliable, and valid instruments HVLT-R and BVMT-R was analysed using a variety of learning indices, adding a comprehending understanding to the performances and their underlying constructs. As part of the data collection process, the patients were well examined within the TOP-study by professional educated and experienced personnel. A limitation of this study is the medication status not accounted for, and it cannot be excluded that this may have had an impact on the results. Some early studies indicated that antipsychotics may have an impact on cognition in schizophrenia (Hill et al., 2004). Other studies revealed significant and stable association between memory impairment and patients with schizophrenia not affected by medication (Aleman et al., 1999). However, this was not within the scope on in the current study to investigate effects of antipsychotics. With respect to the prospective predictive measure of recovery or improving function with the LR, controlling for medication status, and thereby implications of side effect profiles affecting

learning capacity, would have improved the validation of the findings in this study. Herein, an improvement in verbal learning and visual learning, with or without medications, could be investigated using LR, and perhaps reveal different results from previous studies, as LR seems to be more sensitive as a measure of group affiliation.

5. Conclusion

The current thesis demonstrated, as hypothesised, inferior performances in both verbal (HVLT-R) and visual learning (BVMT-R) in patients with schizophrenia, compared to healthy controls. The superiority of performance in healthy controls was present both when using the traditional methods LC, and when using novel methods LR and aggregated LR. Further when comparing the traditional method LC with the novel measure of LR, results showed that LC proved less sensitive to detect significant differences between and within groups, compared to LR. In contrast to the RLS, the LR showed significant ability to detect group affiliation and differences in learning capacity in patients with schizophrenia, in both verbal and visual learning. The RLS did not prove useful in detecting differences in learning ability, in either of the groups. The LR measure appears to be a promising measure for cognitive remedy therapy and vocational training programs, with potential to expand the current understanding of learning in patients with schizophrenia. This should be investigated in future studies.

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