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SIRT1, MMP-9 and TIMP-1 levels in children with specific learning disorder

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ABSTRACT

Background: Specific Learning Disorder (SLD) is a common developmental and neurobiological disorder of childhood characterized by impairment of functionality in one or more areas such as reading, writing, mathematics, listening, speaking, and reasoning. The etiology of SLD is still not fully understood. The aim of this study was to evaluate children with SLD to investigate the potential role of MMP-9, TIMP-1 and SIRT-1, which have important roles in synaptic plasticity, cognitive functions, learning and memory, and are known to be associated with various psychiatric disorders.

Methods: The study was conducted with 44 outpatients aged 8–14 years who were diagnosed with SLD according to DSM-5 in the outpatient clinic and a control group of 44 age, gender and education level-matched healthy children. The groups were compared in respect of serum levels of MMP-9, TIMP-1 and SIRT-1, evaluated using the ELISA method.

Results: Serum MMP-9 levels were significantly lower in children in the SLD group than in the control group, while TIMP-1 was higher. No difference was determined between the groups in respect of the SIRT1 levels. SLD severity was negatively correlated with MMP-9 levels and positively correlated with TIMP-1 levels.

Conclusions: MMP-9 appear to contribute to hippocampal-dependent memory and learning by modulating long-term synaptic plasticity. The findings of this study also reinforce the idea that deregulation of the MMP-9/TIMP-1 ratio may impact learning and play a role in SLD. These findings will help to elucidate the etiology of SLD. Furthermore, understanding molecular pathways can contribute to the discovery of certain biomarkers in SLD pathogenesis and the development of new treatment possibilities.

1. Introduction

Specific Learning Disorder (SLD), which is often referred to as learning disorder or learning disability, is a common neurodevelopmental disorder in childhood characterized by impaired functioning in one or more areas such as reading, writing, mathematics, listening, speaking, and/or reasoning (American Psychiatric Association, 2013). SLD defines a group of specific learning disorders that cannot be explained by intellectual disability, uncorrected visual and auditory problems, other mental, neurological, and motor disorders, inappropriate or inadequate instruction, or psychosocial adversities and deprivations (American Psychiatric Association, 2013). SLD is classified in three types as dyslexia, dysgraphia, and dyscalculia, referring to difficulties in reading, writing, and arithmetic, respectively. It is known to affect 5–15% of school-age children at a severity of mild, moderate or severe (American Psychiatric Association, 2013). Although several theories have been proposed to explain the causes of SLD, the etiopathogenesis is still not fully understood. Genetic causes, biological (structural and functional) disruptions of the central nervous system (CNS), and information processing problems are the most emphasized factors. However, there are currently no laboratory tests that may help to definitively elucidate the etiology (Goswami, 2015).

It has been postulated that childhood-onset neurodevelopmental disorders, including SLD, may be neuroplasticity disorders (Rapoport and Gogtay, 2008; Shaw et al., 2010). Neuroplasticity, a mechanism that enables learning, is defined as the structural and functional changes of neurons and the synapses in the brain in response to various intrinsic or extrinsic stimuli (Citri and Malenka, 2008; Sagi et al., 2012). Sirtuin-1

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(*SIRT1*), Matrix metalloproteinase-9 (MMP-9) and Tissue Inhibitor Matrix Metalloproteinase-1 (TIMP-1) are molecules that have important roles in synaptic plasticity, cognitive functions, learning, and memory (Bach et al., 2018; Herskovits and Guarente, 2014; Jourquin et al., 2005; Knapska et al., 2016; Li et al., 2013; Mich á n et al., 2010). Therefore, these molecules may be implicated in cognitive deficits in SLD, the etiology of which has not yet been fully elucidated.

SIRT1, which is nicotinamide adenine dinucleotide (NAD^+)-dependent, is one of the class III histone/protein deacetylase enzymes. SIRT1 is a well-studied type of sirtuin, which has a wide variety of biological functions, including cell survival, development of the CNS, synapse formation and synaptic plasticity, apoptotic pathways, cognitive functions, learning, and memory (Codocedo et al., 2012; Donmez et al., 2012; Gao et al., 2010; Michan and Sinclair, 2007). It has been reported that SIRT1 has neuroprotective properties and provides resistance against many neurodegenerative diseases such as Alzheimer's, Parkinson's, and motor neuron diseases, and that the expression of the SIRT gene is considerably reduced in neurodegenerative diseases (Donmez and Outeiro, 2013; Jeong et al., 2011). Furthermore, accumulating evidence indicates that SIRT1 could play a critical role in the pathophysiology of psychiatric disorders such as schizophrenia, bipolar disorder, autistic spectrum disorder, depression, and attention-deficit/hyperactivity disorder (ADHD) (Abe et al., 2011; Kishi et al., 2011; Libert et al., 2011; Uzun Cicek et al., 2020).

Matrix Metalloproteinase-9 (MMP-9), an enzyme negatively regulated by SIRT1, is one of the endopeptidases and plays a major role in the degradation and dynamic remodeling of the extracellular matrix (ECM). It has been emphasized that matrix metalloproteinase enzymes (MMPs), which are a large family of extracellular proteolytic enzymes, are involved in many developmental disorders (Brzdak et al., 2017; Wiera and Mozrzymas, 2021) MMP-9 is the best characterized MMP family member to date, and there is strong evidence that similar to SIRT1, MMP-9 is implicated in the pathophysiology of neuropsychiatric diseases such as schizophrenia, bipolar disorder, autism spectrum disorder, neurodevelopmental disorders, stroke, neurodegeneration, and brain tumors (Uzun Cicek et al., 2020; Lepeta and Kaczmarek, 2015; Vafadari et al., 2016). Animal models have suggested that MMP-9 is involved in remodeling the synaptic microenvironment, which may play a role in processes related to brain diseases such as long-term potentiation (LTP), learning and memory, and plasticity (Szepesi et al., 2013; Wang et al., 2008; Wiera and Mozrzymas, 2015). TIMP-1, a tissue inhibitor of MMP-9, is produced by active neurons, and regulates extracellular proteolysis, maintaining the balance between ECM formation and ECM breakdown, which plays an active role in synaptic plasticity (Brew and Nagase, 2010; Okulski et al., 2007). Both components, namely proteolytic MMP-9 and anti-proteolytic TIMP-1, are functionally tightly interconnected and co-active. It has been shown recently that this enzymatic system has a function in dendritic repair, synaptic plasticity, and behavioral learning (Chaillan et al., 2006; Huntley, 2012).

Although emerging evidence suggests that MMP-9 and SIRT1 play an important role in the pathophysiology of neurodevelopmental disorders, there is no study in literature that has examined the link between SLD and SIRT1, MMP-9, and TIMP-1. Therefore, the aim of this study was to determine the serum levels of SIRT-1, MMP-9, and TIMP-1 in children with SLD, to investigate whether these molecules are related to SLD.

2. Subjects and methods

2.1. Participants

The study consisted of 44 children who were diagnosed with "pure" SLD between the ages of 6 and 16 years, and 44 healthy children (without SLD) matched for age, gender, IQ, and socio-cultural factors. Psychiatric evaluation, diagnosis of SLD and classification according to the severity of SLD were made based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria (American Psychiatric Association, 2013). In the SLD group, mild level SLD was determined in 29.5% (n = 13) of the children, moderate level in 34.1% (n = 15), and severe level in 36.4% (n = 16). Children were excluded from the study if they had any chronic medical or neurological disease, eye problems, auditory problems, if they had participated in a similar study in the last 6 months, if they were using drugs with the potential to affect cognitive processes, smoked cigarettes, drank alcohol, or were substance users In addition, children diagnosed with adhd, with adverse conditions such as significant growth-developmental delay, living in conditions of extreme poverty or severe psychosocial deprivation, or with poor quality and/or inadequate education were also excluded to minimize the effects of confounding factors. Conners' Parent Rating Scale-Revised Short Form (CPRS-RS) and DSM-5 criteria were used to eliminate ADHD accompanying SLD.

The study was conducted in the Child and Adolescent Psychiatry Clinic of Cumhuriyet University Hospital and all participants were enrolled in the study between March and December 2019. Written informed consent was provided by the parents/legal guardians of all the participants who agreed to participate in the study, and verbal consent was obtained from each subject. Prior to the initiation of the study, the study protocol was approved by the Local Ethics Committee of Sivas Cumhuriyet University (Date: 05.02.2019, No: 2019–02/04) and the study was performed in accordance with the ethical standards of the Declaration of Helsinki.

2.2. Clinical assessment and neuropsychological measures

To identify the presence of any past and/or present psychiatric disorders in the child, all the children and their parents were evaluated in a semi-structured interview (Turkish version of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children- Present and Lifetime Version, KSADS- PL) (Kaufman et al., 1997; Ü nal et al., 2019). Each child performed the reading test, writing test, mathematics test, clock-drawing test, and right-left discrimination test for evaluation of the reading, writing, and mathematics skills in detail, to measure visual perception and hand-eye coordination, and to determine the SLD subgroup. The Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) (Wechsler, 2003) was applied to all participants to determine the intelligence level and the Stroop test was used to evaluate executive functions (Karakas et al., 1999; Stroop, 1935). The Conners' Parent Rating Scale Revised Short Form (CPRS-RS) was used to eliminate ADHD accompanying SLD (Kaner et al., 2013).

2.3. Biochemical measurements and procedures

Peripheral venous blood samples (10 ml) were taken from each child into vacutainer tubes without anticoagulants between 09:00 and 12:00 a.m. The tubes were kept at room temperature for 10 min, then centrifuged at 3000 rpm for 15 min, and subseequently stored at −80 °C until analysis. Serum concentrations of SIRT1, MMP-9, and TIMP-1 were determined using ELISA (enzyme-linked immunosorbent assay) kits (SinoGeneClon Biotech Co.,Ltd), based on a double sandwich system. The results were reported as μg/L (MMP-9) or ng/ml (SIRT1 and TIMP-1). To minimize analytical variance, all measurements were carried out at the same time following the manufacturer's instructions, and each sample was tested twice. The ELISA plates were read at 450 nm on a microplate reader (TP-Reader-ThermoPlate®) to obtain the optical densities. The standards in the kits were diluted at the specified ratios and the corresponding absorbances were measured, then concentration versus absorbance plots were drawn (Fig. 1a, 1b, 1c). The levels of biochemical parameters in the serum samples were calculated using standard curve graph equations. Sensitivity was defined as 0.18 ng/ml, 10 μg/L, and 0.19 ng/ml for SIRT1, MMP-9, and TIMP-1, respectively. The intra-assay variability for SIRT-1, MMP-9 and TIMP-1 was 5.8%, 4.6%, and 4.5% respectively and the inter-assay variability for SIRT-1, MMP-9, and TIMP-1 was 4.6%, 4.9%, and 5.1% respectively.

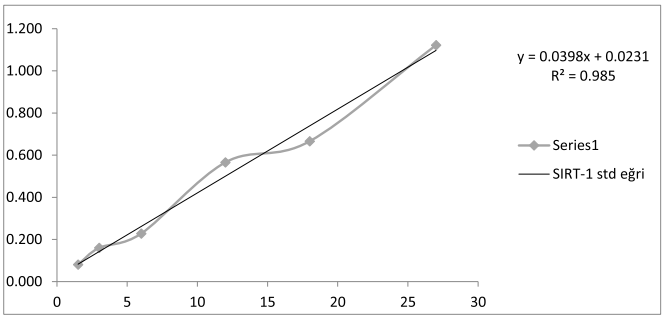

Fig. 1a. SIRT-1 standard curve graph.

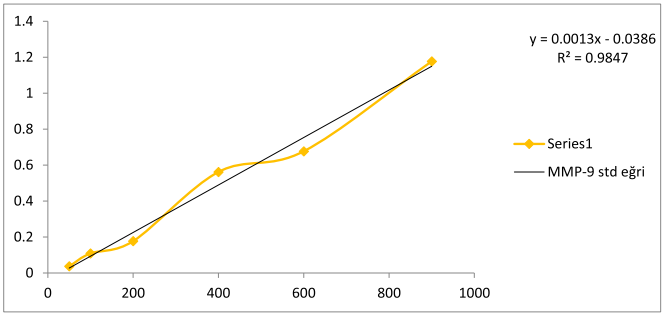

Fig. 1b. MMP-9 standard curve graph.

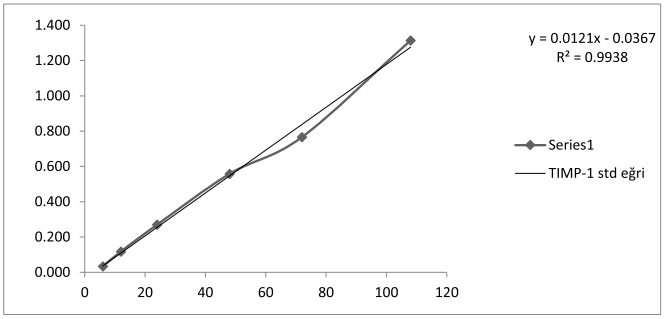

Fig. 1c. TIMP-1 standard curve graph.

2.4. Statistical analysis

The data were evaluated with IBM SPSS 23.0 software (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was performed to determine the normality distribution. The numerical and categorical data were given as mean ± standard deviation (SD), median (min-max) values, number (n), and percentage (%) as appropriate. Comparisons of the groups were performed using the Independent T-test, Man-n–Whitney *U* test, and Kruskal-Wallis test for continuous variables depending on the appropriateness of the statistical assumptions and the Chi-square test was applied to categorical variables. The post hoc non-parametric Dunn's (Bonferroni) and non-parametric Tukey HSD method were performed to understand which groups in the sample differed after the Kruskal Wallis test. A value of $p < 0.05$ was considered statistically significant for all statistical tests.

3. Results

3.1. Demographic characteristics of the participants

The children in both groups comprised 77.3% (n = 34) boys, and 22.7% (n = 10) girls. The mean age of the children was 9.80 ± 2.22 years in the SLD group and 9.84 ± 2.17 years in the control group. The two groups did not differ significantly in terms of age, gender, or family income ($p > 0.05$ for all). The characteristics of the groups are presented in Table 1.

3.2. Results of neuropsychological measures

The children in the SLD group had significantly lower scores in all subscales and the overall level of intelligence (Full Scale Intellectual Quotient (IQ)) of WISC-IV compared to the children in the control group ($p < 0.001$ for all). In the Stroop test, the SLD group children had significantly longer test completion times and showed significantly poorer performance with more errors and corrections than the control group ($p < 0.001$) (Table 2). The scores of all the SLD assessment tests (i.e., reading test, writing test, mathematics test, clock-drawing test, and right-left discrimination test) were significantly lower in children with SLD than in the control group ($p < 0.001$ for all, data not shown).

3.3. Results of biochemical measurements

No statistically significant difference was determined between the two groups in respect of the mean serum levels of SIRT-1 (1.72 ± 0.70 vs. 1.41 ± 0.36; $p = 0.116$) (Fig. 2a) (Table 3). The mean serum levels of MMP-9 were significantly lower in children with SLD than those of the control group (67.45 ± 10.62 vs. 98.23 ± 24.20; $p < 0.001$) (Fig. 2b) (Table 3). The mean serum levels of TIMP-1 were significantly higher in children with SLD compared to the control group (12.44 ± 7.30 vs. 6.37 ± 3.84; $p < 0.001$) (Fig. 2c). (Table 3). The mean serum levels of SIRT1, MMP-9, and TIMP-1 of the groups are shown in Table 3 and Fig. 2.

No significant relationship was determined between the severity of SLD and serum SIRT-1 levels ($p = 0.933$), while a significant correlation was found between serum levels of MMP-9 and TIMP-1 and the severity of SLD. The mean serum MMP-9 levels of children in the mild SLD group were significantly higher than those of the moderate and severe SLD groups, but the levels of the children in the moderate and severe SLD groups were similar ($p < 0.001$). The mean serum TIMP-1 levels of children in the mild SLD group were significantly lower than those of the children in the moderate and severe SLD groups, and the moderate and severe (see Table 4).

4. Discussion

In this study, children with SLD and healthy children were compared in respect of the serum levels of SIRT1, MMP-9, and TIMP-1, which have vital roles in synaptic plasticity, cognitive functions, learning, and memory. The study results revealed that serum MMP-9 levels were significantly lower and TIMP-1 levels were significantly higher in

Table 1
Sociodemographic characteristics of participants.

The study variables	SLD Group (n = 44)	Control group (n = 44)	p-value[a]
Age (mean-years±SD)	9.80 ± 2.22	9.84 ± 2.17	0.879
Gender (n,%)			1.000
Male	34 (77.3)	34 (77.3)	
Female	10 (22.7)	10 (22.7)	
Family Income Level (n,%)[b]			0.135
The minimum wage/less than minimum wage	25 (56.8)	18 (40.9)	
Above the minimum wage	19 (43.2)	26 (59.1)	

Bold font indicates statistical significance: $p < 0.05$.
SD: Standard Deviation; SLD, Specific Learning Disorder.
[a] The chi-square test for categorical variables and the Mann–Whitney *U* test for continuous variables were used to test group differences. Data were given as mean ± standard deviation or number (%).
[b] The level of income was established by the minimum wage value on the date of the study.

Table 2
Comparison of the results of neuropsychological measures.

	SLD group (N = 44)	Control group (N = 44)	p-value[a]
Verbal Comprehension **(mean ±SD)**	99,80 ± 7,24	103,59 ± 9,98	**<0.001**
Perceptual Reasoning **(mean±SD)**	102,57 ± 7,73	111,84 ± 13,78	**<0.001**
Working Memory **(mean±SD)**	80,86 ± 7,90	100,77 ± 8,06	**<0.001**
Processing Speed **(mean±SD)**	88,55 ± 10,38	100,32 ± 6,71	**<0.001**
Full Scale **Intellectual Quotient (mean±SD)**	91,84 ± 11,33	100,80 ± 6,66	**<0.001**
Stroop Test- Total Time Scores (mean- seconds±SD)	136,16 ± 35,74	92,95 ± 19,11	**<0.001**
Stroop Test- Total Error Scores (mean±SD)	3,57 ± 0,89	3,34 ± 1,16	**<0.001**
Stroop Test- Total Correction Scores (mean±SD)	10,75 ± 3,82	3,51 ± 2,88	**<0.001**

Notes.
Bold font indicates statistical significance: P < 0.05.
SD: Standard Deviation; SLD, Specific Learning Disorder.
[a] Independent *t*-test. Data were given as mean ± standard deviation.

Table 3
Mean serum levels of SIRT1, MMP-9, and TIMP-1 in children with SLD and healthy controls.

	SLD group (N = 44)	Control group (N = 44)	p-value[a]
***SIRT1* levels (mean ±SD)**	1.72 ± 0.70	1.41 ± 0.36	0.116
MMP-9 levels (mean ±SD)	67.45 ± 10.62	98.23 ± 24.20	**<0.001**
TIMP-1 levels (mean ±SD)	12.44 ± 7.30	6.37 ± 3.84	**<0.001**

Notes.
Bold font indicates statistical significance: P < 0.05.
MMP-9, Matrix metalloproteinase-9; SD, Standard Deviation; SIRT1, Sirtuin 1; SLD; Specific learning disorder, TIMP-1; Tissue inhibitor matrix metalloproteinase-1.
[a] Mann–Whitney *U* test. Data were given as mean ± standard deviation.

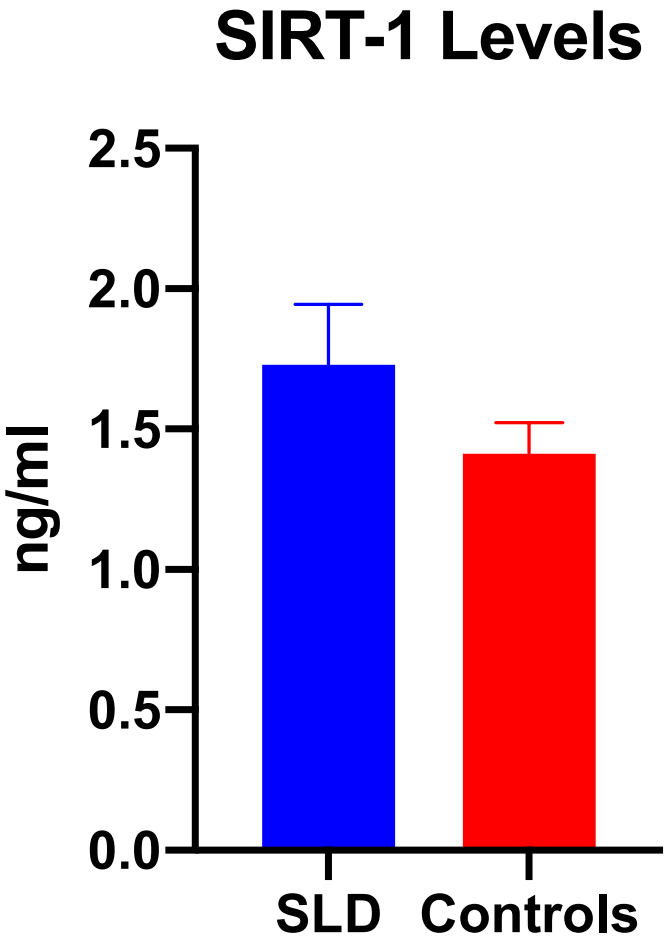

Fig. 2a. The mean serum SIRT-1 levels in children with SLD and healthy controls. Blue column: children with SLD, red column: healthy controls. The mean (SD) serum levels of SIRT-1 did not differ significantly between the two groups (1.72 ± 0.70 vs. 1.41 ± 0.36; p = 0.116).

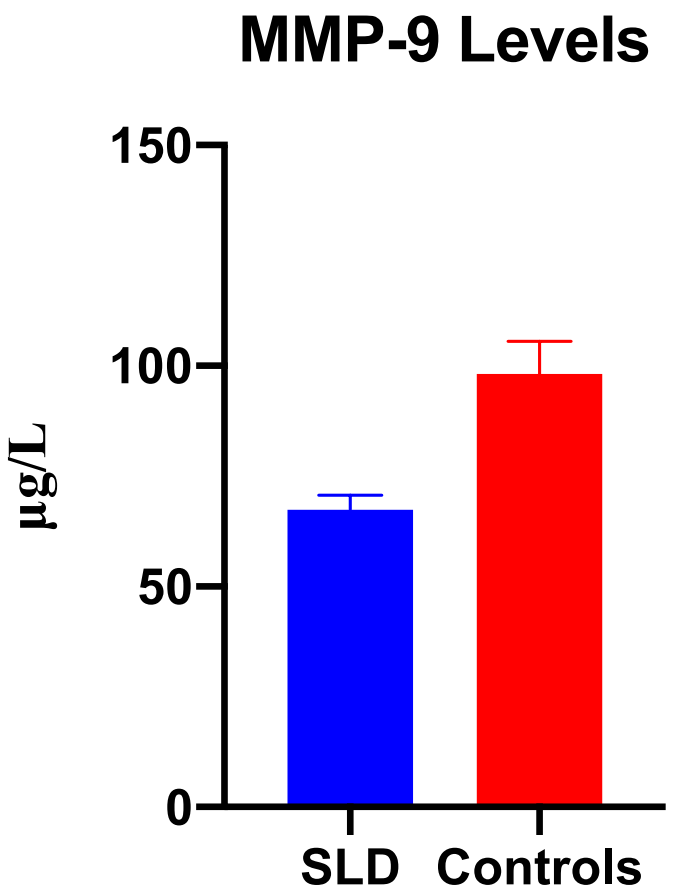

Fig. 2b. The mean serum MMP-9 levels in children with SLD and healthy controls. Blue column: children with SLD, red column: healthy controls. The mean (SD) MMP-9 levels in children with SLD were significantly lower than in the control group (67.45 ± 10.62 vs. 98.23 ± 24.20; p < 0.001).

children with SLD compared to the control group, while serum SIRT-1 levels did not differ between the two groups. Numerous studies have indicated that SIRT-1, MMP-9, and TIMP-1 are involved in a wide variety of physiological and pathological functions. Accumulated evidence suggests that these molecules are also associated with many neuropsychiatric disorders, including cognitive deficits, autism spectrum disorders, ADHD, schizophrenia, Alzheimer's disease, and mood disorders, in addition to learning and memory processes (Abe et al., 2011; Kishi et al., 2011; Libert et al., 2011; Uzun Cicek et al., 2020). However, no previous study has investigated the serum levels of SIRT-1, MMP-9, and TIMP-1 in a paediatric population with SLD, so to the best of our knowledge, this is the first study to have examined the roles of SIRT-1, MMP-9, and TIMP-1 in children with SLD. A common theme and a possible link connecting these molecules to neuropsychiatric disorders is synaptic plasticity (Bach et al., 2018; Herskovits and Guarente, 2014; Knapska et al., 2016).

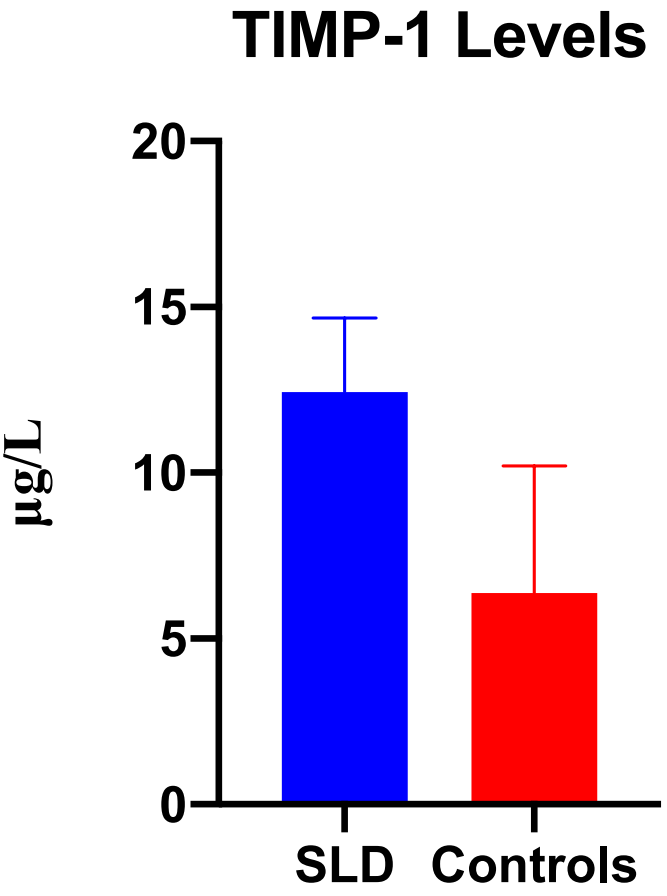

Fig. 2c. The mean serum TIMP-1 levels in children with SLD and healthy controls. Blue column: children with SLD, red column: healthy controls. The mean (SD) TIMP-1 levels in children with SLD were significantly higher than in the control group (12,44 ± 7,30 vs. 6,37 ± 3,84; $p < 0.001$).

Table 4
Comparison of serum levels of Sirtuin-1, MMP-9, and TIMP-1 according to the severity of SLD.

	Mild SLD (n = 13)	Moderate SLD (n = 15)	Severe SLD (n = 16)	p-value[a]
SIRT1 levels (mean ± SD)	1,67 ± 0,65	1,75 ± 0,76	1,74 ± 0,73	0.933
MMP-9 levels (mean ± SD)	77,87 ± 78,27	66,15 ± 8,12	60,20 ± 7,45	**<0,001**
TIMP-1 levels (mean ± SD)	9,38 ± 4,26	12,02 ± 4,76	16,07 ± 9,98	**0,038**

Abbreviations: MMP-9, Matrix metalloproteinase-9; SD, Standard Deviation; SIRT1, Sirtuin 1; SLD; Specific learning disorder, TIMP-1; Tissue inhibitor matrix metalloproteinase-1.

[a] Kruskal Wallis Test was used to test group differences. Data were given as mean ± standard deviation. Bold font indicates statistical significance: $P < 0.05$.

Learning is a process that is defined as the acquisition of understanding, knowledge, behaviors, attitudes, or skills through experience, or being taught. It is now widely known that the learning process occurs through the formation of new axon dendrites in neurons. Therefore, each learning experience means the formation of new synaptic connections (Sagi et al., 2012; Wechsler, 2003). The term "neuroplasticity" is the reconfiguration of synaptic connections and refers to the ability of the neural network in the brain to modify, change and adapt in response to the stimulation of learning, experience, development, or dysfunction (Citri and Malenka, 2008; Sagi et al., 2012). LTP is a persistent increase in synaptic strength and efficacy that originates from long-term high-frequency stimulation of a synapse and is a model of synaptic plasticity. LTP and alterations in neuronal excitability serve as the main substrates for learning, memory acquisition, and storage processes, and represent a basic physiological mechanism of memory storage and arousal/attention (Citri and Malenka, 2008; Sagi et al., 2012; Chan et al., 2016).

However, synaptic plasticity requires structural rearrangement of pericellular and extracellular matrix molecules. ECM molecules in the brain are implicated in regulating synaptic function, plasticity, synaptogenesis and synaptic maturation, and have pivotal roles in neural development and regeneration (Choi et al., 2018). Therefore, there is a reciprocal relationship and interaction among LTP, ECM remodeling, synaptogenesis, and memory consolidation, and this interaction allows the formation of new neural pathways in the brain. The forming of new synaptic connections is encouraged by experiences in environments that lead to learning gain and memory consolidation. Consequently, the morphological and functional plasticity of the synapses involved in learning and memory storage depends on neural activity-dependent changes in synaptic connections and synaptic adhesion between neurons. ECM is also involved in LTP in the hippocampus, a vital structure closely related to learning and memory of the central nervous system through support of the wiring of neuronal networks (Choi et al., 2018; Sykov á and Nicholson, 2008) and it appears to be critical to learning and memory processes. Extracellular proteases selectively cleave to proteins, and structural or signaling molecules within the ECM to stimulate definite signaling pathways that regulate the physiology of the synapse during learning (Dityatev and Schachner, 2003; Sykov á and Nicholson, 2008; Beroun et al., 2019), in addition to playing a crucial role in pathological plasticity (Wiera and Mozrzymas, 2015) MMP-9 is the most extensively studied MMPs family member in the context of synaptic plasticity, learning and memory, and is prevalent in brain areas associated with learning and memory that contain excitatory synapses, and control the NMDA-dependent LTP component (Vafadari et al., 2016; Sonderegger and Matsumoto-Miyai, 2014; Verslegers et al., 2013). Through the effect on spine morphology, MMP-9 appears to be critical in a wide variety of developmental and pathological processes within the CNS, including synaptic plasticity, the consolidation, induction and maintenance of LTP, learning and memory process, neural stem cell proliferation during neurogenesis, repair after brain disorders, and neuropsychiatric diseases (Knapska et al., 2016; Szepesi et al., 2013; Wiera and Mozrzymas, 2015). Numerous studies have noted prominent elevations in the pro and/or active form levels of MMP-9 and following learning different behavioral tasks a significant increase has been shown in the proteolytic activity of MMP-9 in many brain structures including the hippocampus, prefrontal and piriform cortices, nucleus accumbens, and amygdala (Gorkiewicz et al., 2010; Fragkouli et al., 2012; Ganguly et al., 2013). It has also been revealed that MMP-9 knock-out mice show impairments in hippocampal-dependent learning and an impaired LTP, and that LTP is diminished in both magnitude and duration in MMP-9 null-mutant mice (Wright and Harding, 2009; Gorkiewicz et al., 2010, 2015; Ganguly et al., 2013; Nagy et al., 2006). Similarly, blocking MMP-9 activity impairs hippocampal LTP, which plays a role in spatial learning, and abolishes the induction of late-phase LTP (Wang et al., 2008; Gorkiewicz et al., 2015; Mizoguchi et al., 2010). In contrast, the administration of active MMP-9 to MMP-9 knock-out mice restored the magnitude and duration of LTP (Gorkiewicz et al., 2010; Mizoguchi et al., 2010). In the examination of the role of MMP-9 in memory, studies have been conducted in MMP-9 knockout mice using context and cued fear conditioning procedures, and impairment has been observed in hippocampus-dependent contextual fear conditioning and memory (Gorkiewicz et al., 2015; Nagy et al., 2006). It has also been shown that low MMP-9 expression or activity level caused by blocking MMP-9 activity reduces the formation of fear memory (Bach et al., 2018). Consequently, there is evidence suggesting that MMP-9 is needed in learning and memory as an important player in human cognition, whereas blocking the activity of MMP-9 greatly impairs or attenuates

the learning process and memory retention (Sykov á and Nicholson, 2008; Mizoguchi et al., 2010).

MMP-9 activity is inhibited by tissue inhibitor of matrix metalloproteinases (TIMPs) the endogenous inhibitor TIMP-1, through the formation of tight non-covalent complexes with them (Brew and Nagase, 2010; Okulski et al., 2007). Thus, MMP-9 does not work in isolation, but functions as part of a complex network in dynamic balance with TIMP-1. The MMP-9-TIMP-1 enzymatic system is the principal regulator of the ecology of the pericellular environment and is involved in multiple processes and especially in returning the ECM system to a reasonably steady state, thereby actively contributing to learning and memory processes (Wang et al., 2008). Studies have provided evidence that TIMP-1, like MMP-9, is also potentially involved in the molecular and cellular mechanisms of synaptic plasticity and formation of LTP that are required in learning and memory processes (Jourquin et al., 2005; Brew and Nagase, 2010). However, TIMP-1 is not only an MMP inhibitor, but also has independent biological functions such as growth factor activity as a trophic factor and promoting CNS myelination during development, and myelin repair in adulthood (Jourquin et al., 2005; Bozdagi et al., 2007; Nicaise et al., 2019). In TIMP-1 deficient mice, CNS myelination is delayed during postnatal development, and remyelination is impaired after immune-mediated injury in adulthood (Bozdagi et al., 2007).

Studies have also emphasized that the MMP-9/TIMP-1 ratio modulates neuronal plasticity in normal learning and memory processes and is important in developmental and pathological processes occurring in the CNS. In the CNS, the disruption, deregulation, or alteration of the TIMP/MMP-9 balance or ratio impacts ECM-to-cell and cell-to-cell signaling and could provoke several morphological and physiological changes including structural, cellular, and neurochemical alterations such as mossy fiber sprouting, synaptogenesis, changes in expression of BDNF, cell death or neurogenesis. Taken as a whole, an imbalance between MMP-9 and TIMP-1 and changes due to this imbalance could bring about elevated excitability and alterations in neuronal circuitry and are related to behavioral impairments and impaired cognitive functions (Jourquin et al., 2005; Chaillan et al., 2006). In the current study, while there was a negative relationship between the severity of SLD and serum MMP-9 levels, this relationship was the opposite for TIMP-1. Therefore, the findings of this study reinforce the idea that deregulation of the MMP-9/TIMP-1 ratio may impact learning and play a role in SLD.

Another molecule investigated in this study was SIRT1, a NAD^+-dependent histone deacetylase, which is actively involved in diverse complex biological processes and in maintaining brain integrity and neuronal health (Herskovits and Guarente, 2014; Gao et al., 2010; Donmez and Outeiro, 2013). Of these, histone acetylation is an indispensable component of synaptic plasticity and LTP, which are major cellular mechanisms underlying learning and memory, and these are known to be enhanced by histone acetylation (Stetler-Stevenson, 2008). It has been shown that although SIRT-1 expression occurs in many tissues, compared to other tissues, there are significantly higher levels in the brain, in particular, in the hippocampus, which is a pivotal structure for learning and memory (Mich á n et al., 2010; Levenson et al., 2004). To the best of our knowledge, there is no previous study that has investigated the serum SIRT1 level in children with SLD. Nevertheless, in a mouse model of SIRT involvement in histone acetylation, a key component of learning, memory, and synaptic plasticity, it was found that increased histone acetylation leads to sprouting of dendrites and increased number of synapses, improved learning behavior and access to long-term memories (Zakhary et al., 2010). Another animal model study suggested that overexpression of SIRT1 stimulates cognitive developments and has protective effects on memory (Fischer et al., 2007). In addition, molecules such as resveratrol and synthetic SIRT1 activators have been shown to have neuroprotective effects, alleviate hyperactivity and behavioral complaints in autistic patients, and improve cognitive and memory performance (Wang et al., 2017). However, in the current study, no difference was found in the serum SIRT1 levels of children with SLD and children in the control group. Future studies are needed to elucidate the potential role of SIRT1 in the etiology of SLD, to open a new dimension for treatment, and to reveal the effects on learning and memory in the hippocampus. The outcomes of this study present a unique result in the literature to date. Nevertheless, there is still a lack of data about whether these molecules have any role in children with SLD, which prevents adequate comparisons of these results. On the basis of the current study results, in the light of the information summarized above, it can be postulated that MMP-9 and TIMP-1 may contribute to memory and learning by modulating LTP formation and synaptic plasticity, and are thereby implicated in SLD.

4.1. Strengths and limitations

The strengths of this study were that it is the first to have examined the levels of MMP-9, TIMP-1, and SIRT1 associated with cognitive functions in children with SLD, and that the patients were sampled from untreated and non-comorbid settings, leading to better representation of the general population. However, limitations of the study which must be considered can be said to be the limited sample size and that biochemical measurements were not re-measured after a standard special training for SLD. These points restrict the generalizability of the findings.

5. Conclusion

In conclusion, the results of this study indicate that serum levels of MMP-9 and TIMP-1 and the MMP-9/TIMP-1 ratio are altered in children with SLD, and that these two molecules are significantly associated with both the severity of SLD and cognitive functions. These data provide the first evidence for the implication of MMP-9 and TIMP-1 in the etiology and pathophysiology of SLD and learning deficits. Drugs which target MMP-9 and TIMP-1 activity may be promising in the treatment of children with SLD, providing potential therapeutic possibilities. Although it seems possible that MMP-9 and TIMP-1 may contribute to hippocampal-dependent memory and learning by modulating synaptic plasticity, further research with larger samples is needed to replicate, elucidate, and confirm these findings.

Author statement

Cansu Mercan Isik: Term, Conceptualization, Methodology, Writing - Original Draft preparation, Project administration Ayla. Uzun Cicek: Data curation, Writing - Review & Editing, Formal analysis, Project administration. Dilara Ulger Visualization, Investigation, Formal analysis. Sevtap Bakir: Supervision, Investigation.

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Declaration of competing interest

The authors reported no conflict of interests related to this article.

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