DISSERTATION

Behavioral consequences of brain plasticity in musicians – Effects of musicianship on memory integration and temporal discrimination

Behaviorale Konsequenzen der Plastizität des Gehirns bei Musizierenden – Auswirkungen des Musizierens auf Gedächtnisintegration und zeitliche Diskrimination

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Inhaltsverzeichnis

List of figures

List of abbreviations

BF	Bayes factor
GNM	Gesunde Nicht-Musizierende
MBEA	Montreal Battery of Evaluation of Amusia
MD	Musician’s dystonia
NM	Nicht-Musizierende
PM	professionell Musizierende
RT	Reaction time
TDT	Temporal discrimination threshold
TT	Tactile modality in temporal discrimination threshold task
VT	Visual-tactile modality in temporal discrimination threshold task
VV	Visual modality in temporal discrimination threshold task

Abstract

Musical activity is a multimodal activity that has been shown to induce brain plasticity in musicians. These brain changes are often paralleled by positive consequences, such as improved performance in music-related and non-musical cognitive domains. However, brain plasticity induced by musical activity can also be accompanied by negative consequences, as in the case of musician's dystonia (MD), a movement disorder characterized by loss of voluntary muscle control. In two studies, this dissertation investigated the influence of musical activity on two cognitive processes (memory integration & temporal discrimination) on a behavioral level.

Study 1 addressed the question how melodic and visual information is associated with each other and how these associations are integrated into complex cross-modal representations. Since musical activity puts high demand on memory and musical expertise might modulate the underlying memory process, professional musicians and non-musicians were compared using a visual-melodic associative inference paradigm. Participants were tested on their ability to memorize pairs of melody-object pairs and to form integrated representations of these pairs in which melodies are associated with two separate objects across trials. The results showed that musicians had a superior memory performance, although non-musicians also performed above chance level, indicating that they could reliably associate and integrate musical and visual stimuli. The results indicated the existence of two complimentary strategies that support integration of visual-melodic memories and are shaped by musical expertise: Non-musicians rely on an encoding-based mechanism, whereas musicians seem to have access to an additional, more flexible retrieval-based strategy.

Temporal discrimination thresholds (TDT) are elevated in some forms of dystonia and musical activity can improve timing abilities due to the demand to perform precisely timed movements. The question therefore has been raised whether TDT is a suitable biomarker for MD. In study 2, TDTs were compared between MD patients, healthy musicians and healthy non-musicians using a visual, tactile, and visual-tactile paradigm. In addition, associations of TDTs with different potentially influencing factors, such as musical activity, were examined. Results showed that TDTs in MD patients were not different from both control groups, but TDTs in healthy musicians were lower than in healthy non-musicians. Visual-tactile TDTs correlated negatively with age of first instrumental practice in healthy

musicians. Musical training seems to improve temporal discrimination in healthy musicians. No elevated TDTs were observed in MD patients which suggests that TDT is not a reliable biomarker for MD.

Overall, this dissertation shows that musical activity can influence both memory integration of visual-melodic information and TDTs. The results' limitations and implications for future research are discussed for both studies.

Zusammenfassung

Musizieren ist eine multimodale Tätigkeit, die bei Musizierenden zu Hirnplastizität führt. Diese Gehirnveränderungen haben oft positive Folgen, z. B. verbesserte (nicht-) musikalische kognitive Fähigkeiten. Die Hirnplastizität kann negative Folgen haben, wie bei der Musikerdystonie (MD), einer Bewegungsstörung, die mit dem Verlust der willentlichen Muskelkontrolle einhergeht. In zwei Studien wurden in dieser Dissertation Einflüsse von musikalischer Aktivität auf zwei kognitive Prozesse (Gedächtnisintegration & zeitliche Diskrimination) untersucht.

Studie 1 untersuchte, wie Personen Bilder mit Melodien verknüpfen und diese Assoziationen in cross-modale Repräsentationen binden. Da Musizieren hohe Gedächtnisanforderungen stellt und musikalische Expertise den Gedächtnisprozess verändern kann, wurden professionell Musizierende (PM) und Nicht-Musizierende (NM) mit einem visuell-melodischen Assoziationsparadigma verglichen. Teilnehmende sollten sich Objekt-Melodie-Paare merken und diese Paare in übergreifende Repräsentationen binden, sodass Melodien mit je zwei separaten Objekten verknüpft wurden. PM wiesen eine bessere Erinnerungsleistung auf, obwohl NM ebenfalls musikalische und visuelle Informationen verknüpfen und in zusammenhängende Gedächtnisrepräsentationen binden konnten. Die Ergebnisse deuten darauf hin, dass zwei komplementäre Mechanismen die Integration visuell-melodischer Erinnerungen unterstützen, die durch musikalische Aktivität geprägt sein können: NM nutzen eine Strategie, die während des Erlernens der Informationen wirkt. PM können auf eine zusätzliche, flexiblere Strategie zurückgreifen, die während des Gedächtnisabrufs der Informationen zum Einsatz kommt.

Die zeitliche Diskriminationsschwelle (engl.: temporal discrimination threshold, TDT) ist bei manchen Dystonieformen erhöht und Musizieren kann die zeitliche Wahrnehmung verbessern, sodass unklar ist, ob die TDT ein geeigneter MD-Biomarker ist. In Studie 2 wurden TDTs von Personen mit MD, PM und gesunden Nicht-Musizierenden (GNM) mit einem visuellen, taktilen und visuell-taktilen Paradigma verglichen. Ebenso wurden Korrelationen zwischen TDTs und verschiedenen potenziellen Einflussfaktoren (u. a. musikalische Aktivität) untersucht. Die TDTs der MD-Patienten unterschieden sich nicht von beiden Kontrollgruppen, wohingegen die TDTs der PM niedriger waren als der GNM. Bei PM korrelierte das Alter des Instrumentalbeginns negativ mit den visuell-taktilen TDTs. Musikalische Expertise scheint die zeitliche Diskriminationsfähigkeit bei PM zu

verbessern. Bei MD-Patienten wurden keine erhöhte zeitliche Diskriminationsschwelle beobachtet, was darauf hindeutet, dass die TDT kein geeigneter Biomarker der MD ist.

Insgesamt zeigt diese Dissertation, dass musikalische Aktivität die Gedächtnisintegration von visuell-melodischen Informationen und die zeitliche Diskrimination beeinflussen kann. Limitationen und Implikationen der Ergebnisse für zukünftige Forschung werden für beide Studien diskutiert.

1. Introduction

1.1 Musical training as an intensive multimodal and plasticity-driving activity

Making music is a multimodal activity involving a magnitude of different processes. Most obvious, it is a motor activity since complex movement patterns are executed when playing a musical instrument or singing. Auditory processes are involved when listening to the generated tones and monitoring the musical output. Based on this auditory feedback, movements can be adjusted to refine the performance (Altenmüller et al., 2015; Schlaug, 2015). However, musical activity does not only comprise auditory and motor processes, but also critically depends on higher-order cognitive functions, such as attention, learning and memory (Brown et al., 2015; Herholz & Zatorre, 2012). Furthermore, both listening to as well as playing music can influence the mood and elicit strong emotions (Juslin & Laukka, 2004; Koelsch, 2014) and musicians often aim to express and convey emotions when performing (Altenmüller et al., 2015). Lastly, musical activity also has social functions, especially when playing together with others (Koelsch, 2014). Importantly, musical activity is also a cross-modal process involving the interaction and integration of different processes (e.g. motor, auditory, visual processes; Altenmüller et al., 2015; Herholz & Zatorre, 2012).

Professional musicians usually start their musical activity at a young age and invest considerable time practicing to improve their skills. Professional musicianship therefore is a highly specialized skill similar to high performance sports. Hence, the musician's brain has gained special interest within the field of neuroscience and has long been suggested as a model to study experience-driven plasticity (Münte et al., 2002). Several studies have addressed this point and found that intense musical activity can indeed promote experience-driven plasticity and molds the brain (Altenmüller & Furuya, 2016; Herholz & Zatorre, 2012; Münte et al., 2002; Olszewska et al., 2021; Schlaug, 2015), similar to other intensive activities such as juggling (Draganski et al., 2004; Driemeyer et al., 2008), extensive learning (Draganski et al., 2006), playing basketball (Park et al., 2009) or golf (Bezzola et al., 2011). Primarily, structural plastic changes have been found in brain areas of musicians that are directly involved in musical activity. For instance, compared to non-musicians, musicians have been found to have increased volumes in brain areas associated with motor functions (Amunts et al., 1997; Gaser & Schlaug, 2003; Groussard et al., 2014; Hutchinson et al., 2003). Moreover, effects of intense musical training were also found in the auditory system with enlargements in auditory cortices of musicians compared to non-musicians (Bermudez & Zatorre, 2005; Gaser & Schlaug, 2003; Schneider et al., 2002). In addition to these anatomical, structural brain changes, numerous functional brain differences have been documented in musicians (for overviews, see Fauvel et al., 2013; Herholz & Zatorre, 2012).

Effects of musical activity were not only found in motor and auditory regions, but also in brain areas associated with non-musical cognitive processes, such as learning and memory. For example, the hippocampus, a brain structure that is typically involved in learning and long-term memory, has been found to have increased levels of gray matter density and volumes in musicians compared to non-musicians (Groussard et al., 2014; Groussard, La Joie, et al., 2010). Importantly, differences between musically trained and untrained individuals increase with the duration of musical practice and differences were already observable between non-musicians and novice musicians who received musical training for 1–8 years (Groussard et al., 2014). Moreover, musical training does not only result in structural brain differences between musically trained and untrained individuals but can also induce functional plasticity. For instance, a previous study revealed stronger activation in the hippocampus when listening to familiar melodies in musicians compared to non-musicians (Groussard, La Joie, et al., 2010). The authors interpreted this differential activation as indicative of specific memory strategies in musicians. Moreover, professional musicians showed higher activity in the hippocampus than non-musicians in response to an acoustic temporal novelty task (Herdener et al., 2010). These neural responses in the hippocampus were further enhanced in music students who had participated in an intensive auditory skill course. Further studies also revealed that hippocampal volumes predict general fluid intelligence both in expert and amateur musicians, but not in non-musicians (Oechslin, Descloux, et al., 2013) and that the level of musical expertise modulates the degree of changes in brain regions supporting general cognitive abilities such as working memory and attention (Oechslin, Van De Ville, et al., 2013).

In sum, previous studies have shown that musical training can drive plasticity in the brain, in particular in brain regions directly related to making music, but also in areas involved in learning and memory processes (for a review, see also Hoffmann et al., 2020). These changes in the brain often go in hand with positive consequences. For instance, higher performance in various music-related and non-musical cognitive domains have been reported in musicians, such as language skills, memory or executive functions (for overviews, see Barrett et al., 2013; Benz et al., 2016; Fauvel et al., 2013; Schlaug, 2015). The interplay of musical activity with memory functions and a study design to further investigate this interplay is described in more detail in section 1.2. However, the brain changes induced by musical activity are not only beneficial, but can also be maladaptive and have negative consequences, as in the case of musician's dystonia (MD). Section 1.3 focuses on MD as well as aspects of temporal discrimination in both MD patients and healthy musicians.

1.2 Musical activity and musical and non-musical memory functions[1]

Making music involves learning and memory to a large degree. For instance, classical musicians often memorize musical pieces to perform them without sheet music from memory during the concert. Within the jazz genre, musicians usually know the musical form, melody, and harmonic progression of a large repertoire of tunes ("jazz standards"; Hoffmann et al., 2022a, 2022b). This collective knowledge base allows for playing and improvising together in a group. In addition, music making also requires musicians to form associations between information from different modalities and can therefore be considered a cross-modal memory activity (Herholz & Zatorre, 2012; Jäncke, 2019; Talamini et al., 2021). For instance, musicians need to link visual information (i.e. pitch, dynamics or further instructions in the score) with acoustic information and motor processes. Thus, playing a musical instrument at a professional level is a memory-demanding activity, which is mirrored by changes in brain areas typically supporting learning and memory (cf. section 1.1).

Although plasticity effects of musical activity on these learning- and memory-related brain areas have been demonstrated, it is still unclear if musical expertise has an impact on memory performance in general. Recent meta-analyses have addressed the question of

[1] Parts of this section are adapted from the published manuscript (Hoffmann, M., Schmidt, A.*, & Ploner, C. J.* (2022). Musical expertise shapes visual-melodic memory integration. *Frontiers in Psychology, 13,* 1-13. CC-BY 4.0) and the corresponding preprint (Hoffmann, M., Schmidt, A.*, & Ploner, C. J.* (2022). Musical expertise shapes visual-melodic memory integration. bioRxiv.)

skill transfer to non-musical domains and yielded inconclusive results. In a first analysis, Sala & Gobet (2017) investigated skill transfer of musical activity on cognitive and academic performance in children and young adolescents and found a small overall effect and slightly greater effect sizes on intelligence and memory functions. In a second meta-analysis including a larger number of original studies, the authors did not find any impact of musical activity on memory or further cognitive and academic outcomes when quality of studies (i.e. randomization and type of control group) was considered as moderator in the analysis (Sala & Gobet, 2020). These findings and the lack of well-designed studies led the authors of the meta-analysis to conclude that musical training does not have a reliable influence on cognitive skills. However, a recent re-evaluation of the data of Sala & Gobet (2020) refuted these results revealing that musical training can have an effect on general cognitive skills and even induces far transfer effects (i.e. an impact on skills that are not directly related to the trained activity; Bigand & Tillmann, 2022). In line with this, 29 studies with only memory tasks in young adults were included in another meta-analysis and results revealed that musicians had a higher performance in short-term memory and working memory compared to non-musicians (Talamini et al., 2017). Musicians also outperformed non-musicians in long-term memory tasks, although analysis revealed only a small effect size for this memory system. The memory advantage of musicians was furthermore moderated by the type of stimuli: large effect sizes were observed for studies including tonal stimuli. Similarly, a moderate advantage was found for verbal stimuli, whereas small or null effects were reported for visuospatial stimuli. This finding led the authors to conclude that the superior memory performance of musicians is in parts domain-specific (Talamini et al., 2017). One possible explanation, although by far not the only one, for this memory advantage in musicians might stem from active and controlled learning strategies (e.g. chunking, i.e. segmenting information into small, meaningful parts which are then memorized) that are fostered by musical training (Jäncke, 2019; Talamini et al., 2017). That way, musical activity might not only train musical skills, but also support the learning of new skills and transfer to non-musical cognitive abilities, including memory (Altenmüller & Furuya, 2016; Benz et al., 2016; Schlaug, 2015).

Although the positive impact of musical activity on memory function is still under debate, there is another link between music and memory which most people probably know from personal experience regardless of their musical expertise: as described in Hoffmann et al. (2022b), music can be strongly associated with memory and different memories can easily be elicited when listening to specific musical excerpts. Previous research addressed the question why people listen to music. The association of music with memories was described as an important motive for music listening besides regulation of mood and arousal, achievement of self-awareness and expression of social relatedness (Laukka, 2007; Lonsdale & North, 2011; Schäfer et al., 2013). In line with the intuitive notion of a strong relationship between music and memory, empirical studies have shown that music can elicit vivid, perceptually detailed non-musical memories of previously experienced events in both healthy persons and individuals with memory impairments (Belfi et al., 2016; El Haj et al., 2012; Janata et al., 2007). Importantly, not only memories of experienced events, but various different non-musical information can be associated with and reactivated by music, such as semantic memories, emotions or motor programs (Jäncke, 2019; Koelsch, 2015). In an influential modular model of music processing, the "musical lexicon" is described as one module that includes representations of the melodies one has encountered across the lifespan (Peretz & Coltheart, 2003). The musical lexicon is linked to an "associative memories" module, including non-musical information that can be evoked by listening to specific melodies depending on the contextual demands. Beyond building direct links with non-musical information, music seems therefore also to support binding of distinct non-musical memories into cross-modal memory representations (Hoffmann et al., 2022b).

The process of integrating memories from events or episodes that are related but were not experienced together into an overlapping memory network is called memory integration (Schlichting & Preston, 2015; Zeithamova, Schlichting, et al., 2012) and plays an important role in organization of episodic memories and formation of networks between related memories (Duncan & Schlichting, 2018; Zeithamova et al., 2019). In addition, memory integration is also involved in a range of different non-mnemonic processes (e.g. decision making, spatial navigation and creativity; Duncan & Schlichting, 2018; Schlichting & Preston, 2015; Zeithamova et al., 2019; Zeithamova, Schlichting, et al., 2012). A paradigm that is typically used to study memory integration is the associative inference task (Zeithamova, Schlichting, et al., 2012). In this task, participants study pairs of stimuli (e.g., a pair of stimulus A and stimulus B). Some of the pairs overlap with stimuli of other pairs (e.g., stimulus B is also associated with stimulus C), i.e. they share a stimulus (B) so that two distinct stimuli (i.e. stimuli A and C) become associated with one common stimulus. This task does not only assess the ability to memorize pairs of stimuli, but also to form integrated representations of associated stimulus pairs (i.e. of AB- and BC-pairs) and infer indirect relationships between stimuli of this integrated memory representation (i.e. AB- and BC-pairs, hence AC). Previous studies have suggested that different strategies support the formation of integrated memories either during encoding or retrieval of the underlying memory episodes (Duncan & Schlichting, 2018; Shohamy & Daw, 2015; Zeithamova, Schlichting, et al., 2012; Zeithamova & Preston, 2010) and that analyzing both accuracy (i.e. percentage of correct answers) and reaction times (RTs) in associative inference tasks can shed light on the underlying cognitive processes (Pajkert et al., 2017; Schlichting et al., 2014; Shing et al., 2019).

Previous studies mainly used visual stimulus material. As outlined in Hoffmann et al. (2022b), little is known how musical and visual information is bound into complex cross-modal representations and this question has rarely been addressed in previous research. Since musical memory might differ from other memory modalities both on the behavioral (Cohen et al., 2009, 2011) and neural level (Esfahani-Bayerl et al., 2019; Finke et al., 2012; Groussard, Rauchs, et al., 2010; Groussard, Viader, et al., 2010), it is conceivable that the integration process of musical and visual stimuli might differ from purely visual information. In addition, this process might be modulated by musical expertise given the memory demands of musical activity and the structural and functional brain changes induced by musical training. The aim of the first part of this dissertation therefore was to investigate the ability of professional musicians and non-musicians to associate melodies with visual objects and to form complex representations of melodies with two separately studied visual objects (Hoffmann et al., 2022a, 2022b). A visual-melodic variant of an associative inference task (Pajkert et al., 2017; Preston et al., 2004; Shing et al., 2019; Zeithamova, Dominick, et al., 2012; Zeithamova & Preston, 2010) was used to compare musicians and non-musicians in how visual and musical information is associated and integrated.

1.3 Musician's dystonia, musical activity, and temporal discrimination thresholds[2]

Brain changes induced by intensive and prolonged musical activity can also have negative consequences. This is the case in musician's dystonia (MD), a task-specific neurological movement disorder that can occur when extensively training fine movements. It manifests by the loss of voluntary control and inability to coordinate muscles while playing the instrument (Altenmüller et al., 2012; Altenmüller & Jabusch, 2010). It has been suggested that one cause of MD is maladaptive neural plasticity which means that the brain changes induced by intensive musical practice progress too far in patients with MD, eventually leading to dystonic symptoms (Altenmüller et al., 2012; Lin & Hallett, 2009). Brass and wind players usually develop MD in the embouchure with impaired control of lips, tongue and facial muscles (Frucht, 2009). In musicians of other instrument groups (e.g. piano, violine, guitar), MD usually affects the fingers, hands or arms (Altenmüller & Jabusch, 2010). It affects about 1–2% of professional musicians (Altenmüller & Jabusch, 2010) and often terminates the professional musical career (Altenmüller et al., 2015; Altenmüller & Jabusch, 2010).

Although the disease model of MD is not fully understood, the pathophysiology and causes of MD seem to be multifactorial (Altenmüller & Jabusch, 2010; Stahl & Frucht, 2017). Neuroimaging and electrophysiological studies have identified abnormalities throughout the brain in patients with MD or other types of focal dystonia (Lin & Hallett, 2009). These pathophysiological findings include:

(i) deficient inhibitory mechanisms in the motor system leading to unintended activation of surrounding muscles (Sohn & Hallett, 2004);

(ii) alterations in sensory perception and sensorimotor integration with difficulties in temporal and spatial sensory discrimination (Bara-Jimenez, Shelton, & Hallett, 2000; Bara-Jimenez, Shelton, Sanger, et al., 2000) as well as enlarged and disorganized receptive fields in somatosensory cortex (Bara-Jimenez et al., 1998; Elbert et al., 1998) in patients with different forms of focal dystonia. However, a

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[2] Parts of this section are adapted from Borngräber, F.*, Hoffmann, M.*, Paulus, T., Junker, J., Bäumer, T., Altenmüller, E., Kühn, A. A., & Schmidt, A. (2022). Characterizing the temporal discrimination threshold in musician's dystonia. *Scientific reports*, *12*(1), 14939. CC-BY 4.0.

recent study did not find any evidence for abnormal finger representations in the sensorimotor cortex in a group of MD patients (Sadnicka et al., 2022);

(iii) maladaptive plasticity, i.e. the beneficial neural adaptations in response to repeatedly practiced movements progress too far in MD leading to uncontrolled disorganization of the sensorimotor cortex and eventually to dystonic movements (Lin & Hallett, 2009; Rosenkranz et al., 2005).

In addition to these pathophysiological mechanisms, previous research has identified risk factors and predispositions contributing to the manifestation of MD (Altenmüller & Jabusch, 2010; Stahl & Frucht, 2017). Different extrinsic factors have been described that might trigger the development of MD, such as the workload or spatial and temporal demands associated with playing the respective instrument. In keyboard or plucked instrument players, for instance, dystonia more often appears in the right hand, whereas in string players the left hand (i.e. the hand that has to perform more precise and faster movements**)** is typically affected (Altenmüller et al., 2012; Jabusch & Altenmüller, 2006). Also, high string players (e.g. violin players who often have to play more virtuosic parts with small, precise and fast movements) are more often affected than low string players (e.g. cello or double bass players; Altenmüller et al., 2012; Jabusch & Altenmüller, 2006; Rozanski et al., 2015). In addition, classical musicians seem to be at a higher risk for developing MD compared to jazz or pop musicians (Jabusch & Altenmüller, 2006). A possible explanation for this finding is that classical music might pose higher musical and social constraints on musicians who mainly reproduce music that is often familiar to the audience, whereas in the pop or jazz genre musicians are rather free to improvise with less musical constraints (Altenmüller & Jabusch, 2010; Jabusch & Altenmüller, 2006). A late begin of instrumental practice (Schmidt et al., 2013) and intensified musical practice (Altenmüller & Jabusch, 2010; Schmidt et al., 2009) have been described as further risk factors. Furthermore, increased levels of anxiety, perfectionism and neuroticism have been found in patients with MD (Enders et al., 2011; Ioannou & Altenmüller, 2014; Steinlechner et al., 2018), indicating that these psychological factors might also trigger or might be a comorbidity of MD. Local pain, overuse, nerve-entrapment and traumatic injuries have been described as further risk factors (Altenmüller & Jabusch, 2010). Importantly, MD seems also to have a genetic component, since a positive family history of dystonia is reported in up to a third of MD patients (Altenmüller, 2003; Schmidt et al., 2011) and a familial clustering of dystonia has been described (Schmidt et al., 2006, 2009). Recent studies identified first potential genetic risk factors (Hebert et al., 2017; Lohmann et al., 2014). Figure 1 displays the current pathophysiological model illustrating the complex interplay of predisposition and risk factors: Different intrinsic and extrinsic risk factors can trigger the onset of musician's dystonia based on a genetic predisposition, i.e. the endophenotype that is characterized by the abovementioned neurophysiological abnormalities (Altenmüller et al., 2012; Altenmüller & Jabusch, 2010; Schmidt & Altenmüller, 2019).

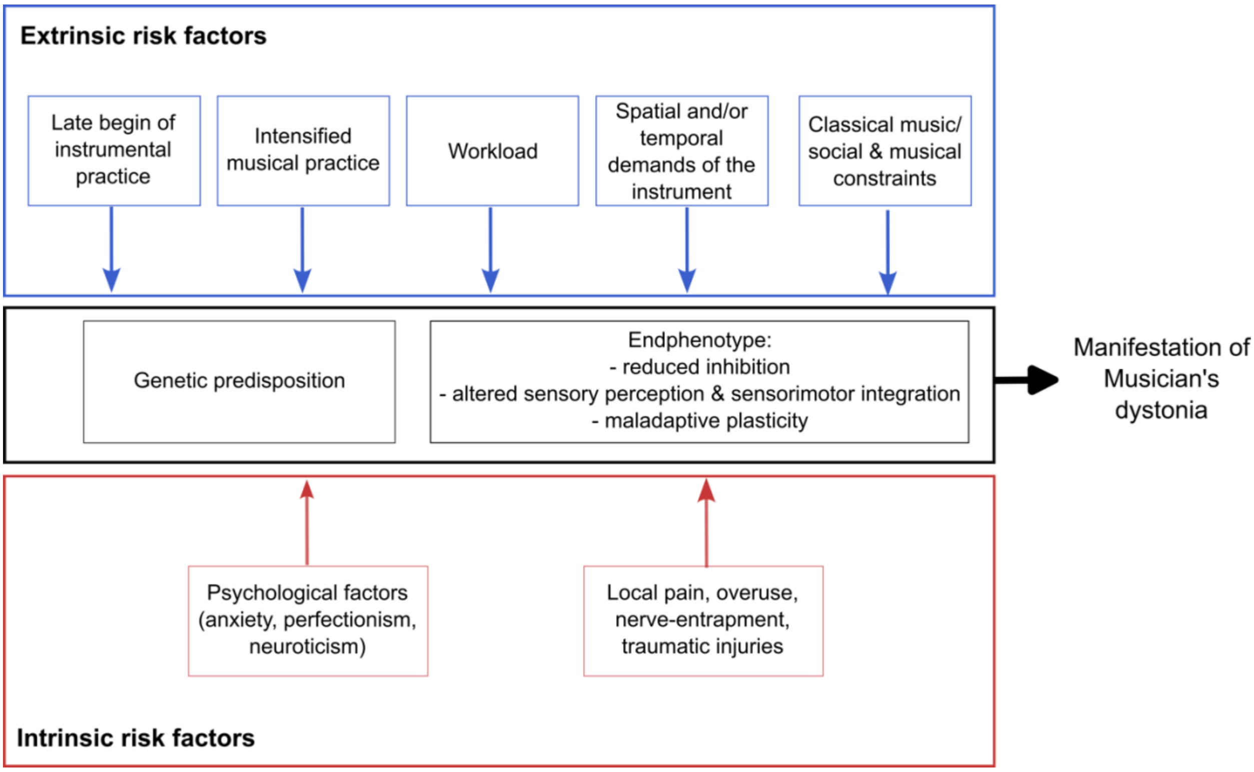

Figure 1. Current pathophysiological model of musician's dystonia (MD). Extrinsic (upper panel) and intrinsic (lower panel) risk factors that can trigger the onset of MD based on predisposition. Own illustration based on data and figures from Altenmüller et al. (2012), Altenmüller & Jabusch (2010) and Schmidt & Altenmüller (2019).

As current priorities in dystonia research (including MD), a better understanding of the genetic and environmental influences as well as the development of better diagnostic criteria and tests have been identified (Pirio Richardson et al., 2017; Smit et al., 2021). A promising avenue for achieving these goals is the identification of biomarkers that can reliably discriminate between affected and unaffected persons. As outlined in Borngräber et al. (2022), one potential biomarker that has been investigated in numerous studies is the temporal discrimination threshold (TDT). The TDT is defined as the shortest time interval at which two stimuli can be identified as asynchronous (Bradley et al., 2009). The

TDT has been found to be elevated in patients with different forms of dystonia (Bradley et al., 2012; Fiorio et al., 2003; Kimmich et al., 2011; Scontrini et al., 2009) and seems to be a sensitive marker of deficient sensory processing and abnormal sensory integration in the basal ganglia (Bradley et al., 2009, 2012). Interestingly, abnormal TDT levels have also been shown in unaffected first-degree relatives of patients with different types of focal dystonia (Bradley et al., 2009; Kimmich et al., 2011, 2014), indicating that the TDT might also be a potential endophenotype that can help to identify persons who have a genetic predisposition for MD but are not affected. Thus, a sensitive endophenotype could help to detect gene carriage in unaffected relatives and be useful to unravel so far undiscovered genetic causes (Bradley et al., 2009).

As outlined in Borngräber et al. (2022), the potential of TDT as a biomarker in MD has also been investigated. Previous studies found a relatively low frequency of abnormal TDTs in patients with MD (Killian et al., 2017) and did not reveal any difference between TDTs in patients with MD and healthy control participants (Maguire et al., 2020). It has been suggested that these findings might be due to the superior timing abilities that have been found in healthy musicians in both visual and auditory domains and probably are a consequence of long-time musical training (Rammsayer et al., 2012). Moreover, basic timing abilities seem to be intact in musicians suffering from MD in both auditory perceptual and sensorimotor synchronization tasks (van der Steen et al., 2014). Thus, the improved timing abilities might also have enabled MD patients to perform relatively normal in the TDT task (Maguire et al., 2020). The results of these previous studies have raised the question whether TDT can be a suitable biomarker for MD.

As described in Borngräber et al. (2022), the previous studies have two main limitations: First, both studies assessed TDTs only in the visual domain (Killian et al., 2017; Maguire et al., 2020). It might be an asset to measure TDT not only in the visual, but also in the tactile domain, since abnormal spatial and temporal discrimination has been found in patients with focal hand dystonia (Bara-Jimenez, Shelton, & Hallett, 2000; Bara-Jimenez, Shelton, Sanger, et al., 2000). Moreover, it is not clear whether musical activity influences different domains to the same degree, so that examination of TDTs in different modalities seems mandatory in order to gain a better understanding of TDT in healthy musicians, MD patients and healthy non-musicians.

As a second limitation, in one of the previous studies both groups of non-affected individuals (i.e. healthy musicians and healthy non-musicians) were combined in the control group (Maguire et al., 2020). This is problematic since timing performance is a central capacity of musical ability, as musicians often have to perform precisely timed movements, especially when playing with others. Accordingly, compared to non-musicians, musicians have been found to perform better in both visual and auditory perceptual timing tasks, including temporal discrimination tasks (Rammsayer et al., 2012; Rammsayer & Altenmüller, 2006). Similarly, musicians also show improved abilities in temporal production, including finger tapping and rhythm synchronization tasks (Bailey & Penhune, 2012; Janzen et al., 2014). Improved timing abilities might also be related to plasticity effects, since enlarged cortical representations in both the somatosensory and auditory domains have been documented in musicians with long-lasting, extensive musical training (Pantev et al., 2001). It therefore seems important to have both healthy musicians and non-musicians as separate reference groups when evaluating TDTs in MD.

The aim of the second part of this dissertation therefore was to investigate the effect of musicianship and MD on TDTs. To this end, TDT of healthy musicians, MD patients and healthy non-musicians were compared in three modalities to evaluate the reliability of the TDT as a biomarker in MD. As a secondary aim, TDTs of dystonic and non-dystonic hands and fingers were compared in MD patients and associations of TDTs with potentially influencing factors (i.e. musical activity, disease-variables, personality profiles) were investigated in healthy musicians and musicians with MD.

1.4 Aims of the dissertation

As outlined above, musical activity induces structural plasticity in the brain and can be accompanied by both positive but also negative consequences. This dissertation addressed several open questions and investigated how musical activity influences two basic cognitive processes on a behavioral level:

1) Is there an influence of musicianship on memory integration of musical and visual information?
2) Is there an influence of musicianship on TDTs and how are TDTs influenced by MD? Are TDTs furthermore associated with different potentially influencing factors (i.e. musical activity, disease variables and personality profiles)?

In order to answer the research questions, two studies were conducted and published in two separate publications that form the basis of my cumulative dissertation:

1) Hoffmann, M., Schmidt, A.*, & Ploner, C. J.* (2022). Musical expertise shapes visual-melodic memory integration. *Frontiers in Psychology, 13,* 1–13. https://doi.org/10.3389/fpsyg.2022.973164
   * These authors contributed equally.
2) Borngräber, F.*, Hoffmann, M.*, Paulus, T., Junker, J., Bäumer, T., Altenmüller, E., Kühn, A. A., & Schmidt, A. (2022). Characterizing the temporal discrimination threshold in musician's dystonia. *Scientific reports*, *12*(1), 14939. https://doi.org/10.1038/s41598-022-18739-y
   * These authors contributed equally.

2. Methods & results

In order to increase comprehensibility, I first describe both methodology and results of study 1 and then for study 2. In the respective results sections, only the main results are included in this dissertation. Additional results are reported in the respective publications (Borngräber et al., 2022; Hoffmann et al., 2022b). Both studies were approved by the Ethics Committee of the Charité – Universitätsmedizin Berlin and conducted in conformity with the Declaration of Helsinki. All participants gave written conformed consent prior to study participation and received financial reimbursement for study participation.

2.1 Study 1: Influence of musical activity on visual-melodic memory integration[1]

2.1.1 Methods

Participants:

The final sample consisted of two groups: professional musicians (*n* = 30) and non-musicians (*n* = 30). The group of professional musicians included instrumental musicians who still studied at a music school or university or who had already finished their studies and worked as professional musicians. The group of non-musicians included persons who had participated never or only for a short time in extracurricular musical activities. Importantly, all participants in the non-musician group who had participated in musical activity had stopped with it at least 10 years prior to study participation. Further inclusion criteria were no reported neurological or psychiatric disorders and scoring within the normal range in a test of basic perceptual abilities of music (i.e. the Scale subtest of the Montreal Battery of Evaluation of Amusia (MBEA); Peretz et al., 2003). The two groups were matched for sex, age and education and had comparable levels of non-verbal intelligence (for detailed demographics and information on musical activity, see Table 1 in Hoffmann et al., 2022b). Further information on the recruitment of participants, sample size determination and assessment of musical activity can be found in Hoffmann et al. (2022b).

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[1] Parts of this section are adapted from the published manuscript (Hoffmann, M., Schmidt, A.*, & Ploner, C. J.* (2022). Musical expertise shapes visual-melodic memory integration. *Frontiers in Psychology, 13,* 1-13. CC-BY 4.0) and the corresponding preprint (Hoffmann, M., Schmidt, A.*, & Ploner, C. J.* (2022). Musical expertise shapes visual-melodic memory integration. bioRxiv.)

Experimental task:

A musical associative inference task with visual and melodic stimuli was administered. The task is an adaption of a visual associative inference task, a paradigm that is typically used to investigate memory integration and has been used in both behavioral and fMRI studies with healthy participants of different age groups and clinical populations (Pajkert et al., 2017; Preston et al., 2004; Shing et al., 2019; Zeithamova & Preston, 2010). The task comprised three cycles, each consisting of one encoding and retrieval block. Between each encoding and retrieval block, a 5-minute delay was included. The overall task structure is displayed in Figure 2A.

Encoding: During each encoding block, participants studied overlapping pairs of melodies and objects, so called AB- and BC-pairs. This means that participants viewed an object (the A-stimulus) on the computer screen and heard a melody (the B-stimulus) at the same time. In another pair, that was presented at a later timepoint during the same encoding block, the B-melody was played again. This time it was paired with another object (the C-stimulus). Thus, the AB- and BC-pairs were overlapping, i.e. they shared the same melody (the B-stimulus) which linked the two objects (A- and B-stimuli) from distinct trials. DE-pairs were included as a control condition. All DE-pairs consisted of one object and one melody which were not linked to another object (i.e. DE-pairs were non-overlapping). Per encoding block, 18 trials (i.e. object-melody pairs) were presented (six AB-, six BC-, six DE-pairs). An example of the encoding procedure is depicted in Figure 2B.

Retrieval: The subsequent retrieval block consisted of two parts: In the first part, participants were tested on indirect AC-trials. This means that an object (A-stimulus) was shown in the upper part of the computer screen and two further objects (C-stimuli) in the lower part. Participants were asked to choose the object (C-stimulus) that had been paired with the same melody as the upper object (A-stimulus). Following the terminology of previous studies (Pajkert et al., 2017; Schlichting et al., 2014; Shing et al., 2019; Zeithamova & Preston, 2010), these trials were termed “indirect trials” since the two objects were not directly presented together but were indirectly associated via the common melody (the B-stimulus). Afterwards, the direct retrieval phase started, in which participants were tested for their memory of the object-melody pairs they studied in the encoding phase. Here, participants perceived two objects (two A-, C- or E-stimuli) on the screen and a melody (B- or D-stimulus) and had to indicate which of the two objects was presented together with the melody during the encoding (see Figure 2B for an example of the retrieval block). In line with earlier studies (Pajkert et al., 2017; Schlichting et al., 2014; Shing et al., 2019; Zeithamova & Preston, 2010), these trials were termed “direct trials” since the direct association of objects and melodies was tested as they were studied. Further details on the task and its administration are described in Hoffmann et al. (2022b).

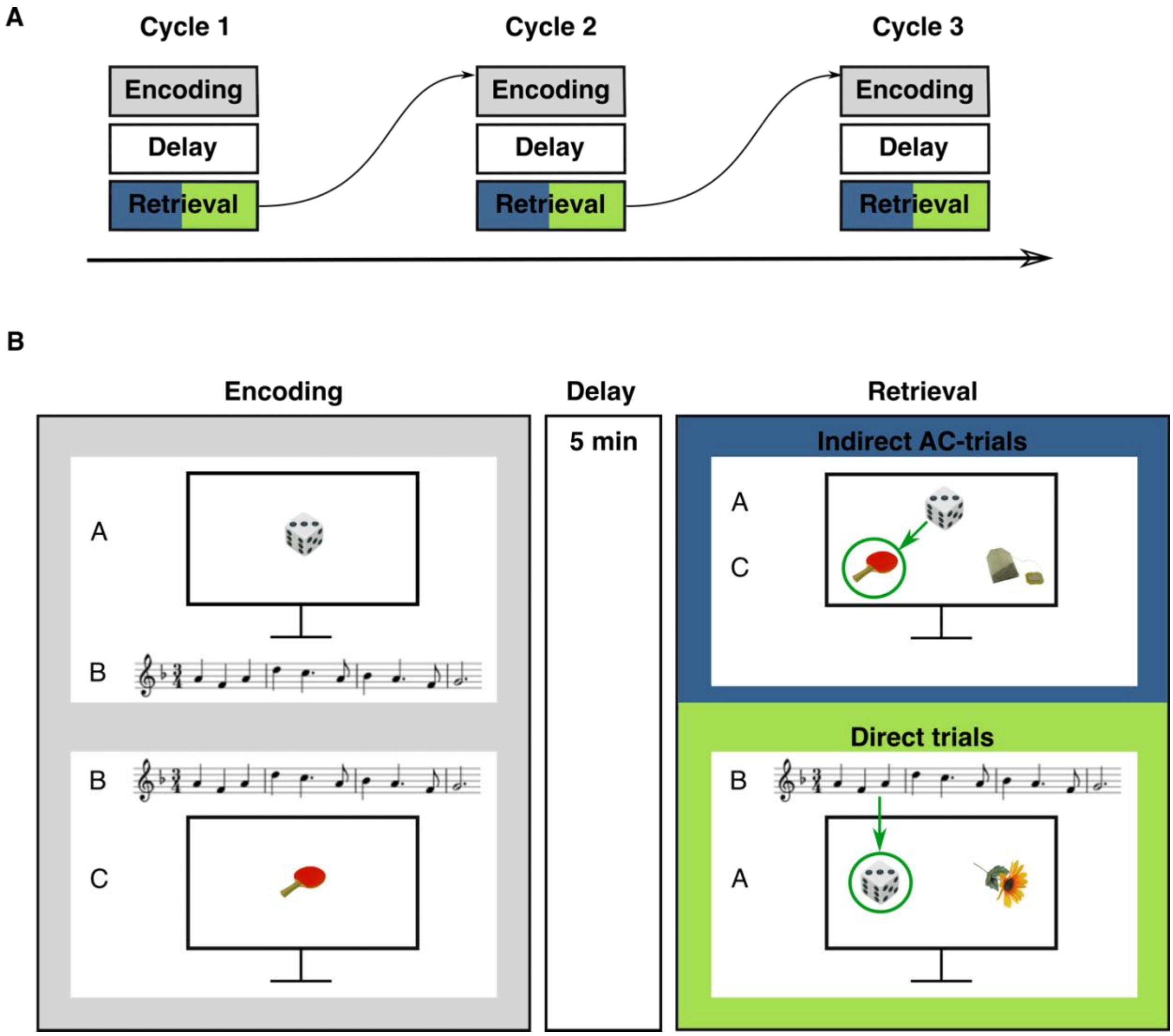

Figure 2. Structure & examples of the visual-melodic associative inference paradigm. (A) The task comprised three cycles with one encoding and retrieval block per cycle. Between each encoding and retrieval block, a delay of 5 minutes was included. Encoding and retrieval blocks were presented in alternating order. (B) In the encoding block, pairs of objects and melodies were presented. Some of the pairs were overlapping (AB-/BC-trials), i.e. they shared the common melody. Additionally, non-overlapping DE-pairs were presented, that were not linked to another pair (DE-trials are not shown in the Figure). During the retrieval, memory for direct AB-, BC- and DE-trials (i.e. studied object-melody associations) and for indirect AC-trials (i.e. object-object pairs that were associated via the common melody) was tested. The respective correct choice is indicated by the green arrow. Figure adapted from Hoffmann et al. (2022b).

Visual and melodic stimuli:

Visual stimuli consisted of 331 images of everyday objects. All visual stimuli were taken from the Bank of Standardized Stimuli (BOSS Phase II; Brodeur et al., 2014). The pool of musical stimuli consisted of 43 melodies taken from diverse genres and presented in a piano tune without orchestration or lyrics. Musical stimuli varied in length (range = 5–10 s, mean duration = 5 s) so that the musical phrase was contained, and the tempo not artificially changed. Importantly, length of melodies did not predict whether direct trials were answered correctly or incorrectly (for detailed results see Hoffmann et al., 2022b). Melodies were tested for recognition in a pilot test with participants who differed in their levels of musical activity and excluded if recognized by a high percentage of participants. Melodies were further evaluated for recognition during the proper experiment. Only a small number of participants indicated to recognize few melodies. More detailed information on the melodies and especially on their evaluation can be found in Hoffmann et al. (2022b).

Statistical Analysis:

The main dependent variables were accuracy and reaction times (RT) which were compared between groups and trial types. Accuracy refers to the percentage of correct responses. RTs were analyzed only for correctly answered trials and summarized by medians. Both accuracy and RTs were calculated per trial type and data were collapsed across cycles. Since data was mostly non-normally distributed, non-parametric analyses were conducted using R (version 3.6.3; R Core Team, 2020). For the main analysis of accuracy and RTs, repeated measures ANOVAs for non-normally distributed data were conducted using the R-package MANOVA.RM (Friedrich et al., 2019, 2021). Wald-type statistics (WTS) and permuted *p*-values were calculated. In case of a significant interaction, pairwise comparison were conducted using the MANOVA.RM package for the within factor trial type and the package GFD (Friedrich et al., 2017) for comparisons between the groups. In all post-hoc analyses, Bonferroni-Holm (Holm, 1979) correction was applied to adjust *p*-values for multiple pairwise comparisons. In addition, Kendall's τ were calculated to examine correlations between accuracy in direct and indirect trials.

2.1.2 Results

Accuracy:

All direct trial types (i.e. AB-, BC- and DE-trials) were pooled for data analysis, since there was no difference between overlapping trial types (i.e. AB- and BC-pairs) and non-overlapping DE-pairs and since this approach was also adopted in previous studies (Pajkert et al., 2017; Zeithamova & Preston, 2010). First, accuracy in both trial types in musicians and non-musicians was tested against the 50% chance level using Wilcoxon signed rank tests (cf. also Figure 3A). Results showed that both musicians and non-musicians performed above chance level in both trial types. In a first ANOVA analysis, accuracy was compared between group and trial types. Results revealed a significant group effect indicating that musicians performed better than non-musicians across trial types. The effect of trial type and the interaction of group and trial type were not significant. Figure 3A shows the results for the performance in the two groups and trial types. Detailed statistical results are reported in Hoffmann et al. (2022b).

Reaction times:

Next, RTs of correctly answered trials were compared between groups and trial types. Both the main effect of group and the main effect of trial type were not significant. Results revealed a significant interaction of group and trial type. For post-hoc tests, the two levels of both factors (i.e. group, trial type) were compared, respectively. For non-musicians, the post-hoc tests revealed a significant difference between trial types with shorter RTs in indirect than in direct trials. No difference between RTs in the two trial types was found in musicians. Comparing trial types post-hoc between groups did not reveal any differences for both indirect and direct trials. Figure 3B shows data of RTs for musicians and non-musicians in both trial types. Detailed statistical results are reported in Hoffmann et al. (2022b).

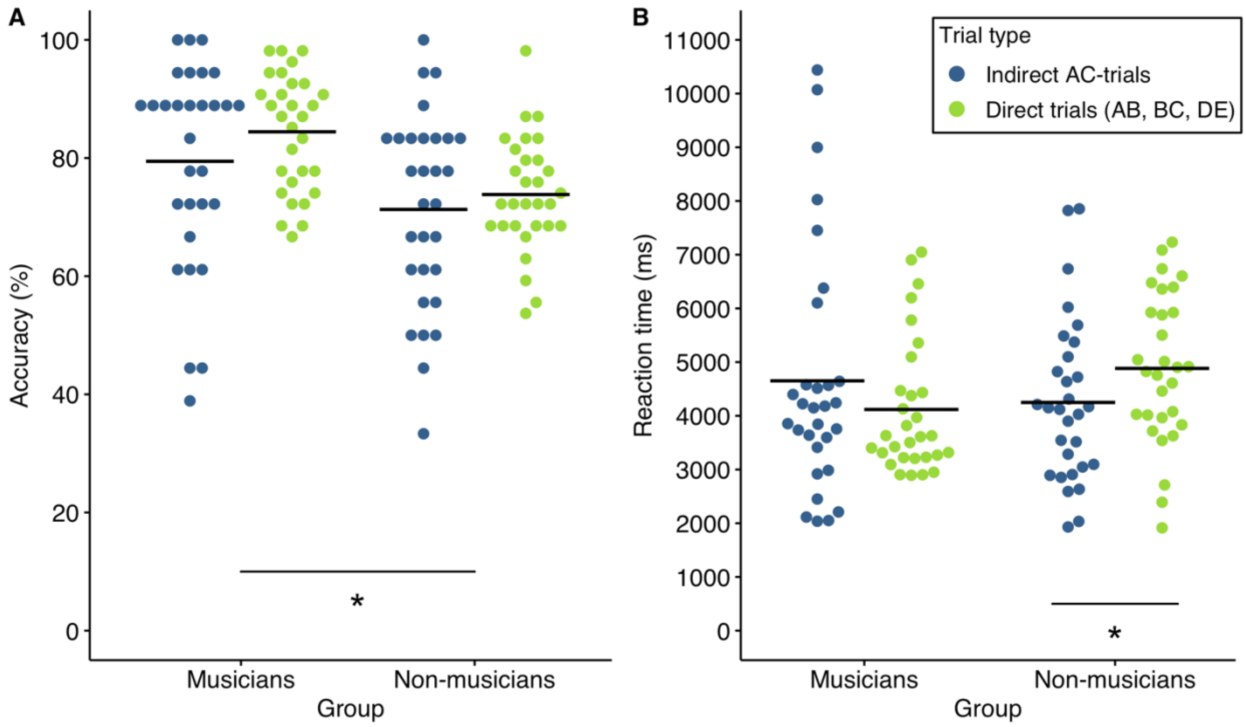

Figure 3. Accuracy and reaction times (RTs) of musicians and non-musicians in direct trials (AB, BC & DE) and indirect AC-trials. (A) Accuracy (i.e. percentage of correct answers) in both trial types and groups. The asterisk marks the significant group effect. (B) RTs in both trial types and groups. Only RTs of correctly answered trial types are displayed and are given in milliseconds (ms). The asterisk marks the significant post-hoc comparison of trial types in the non-musician group. Solid lines mark the respective mean. Figure adapted from Hoffmann et al. (2022b).

Correlation analyses:

Correlations of accuracy in indirect (AC-) trials with accuracy in overlapping direct (i.e. AB & BC) trials were furthermore analyzed. Significant correlations of accuracy in AC-trials with both AB- and BC-accuracy were found in musicians. In contrast, no significant associations of AC- with AB- or BC-accuracy were found in non-musicians (see Figure 4 for detailed results of the correlation analyses).

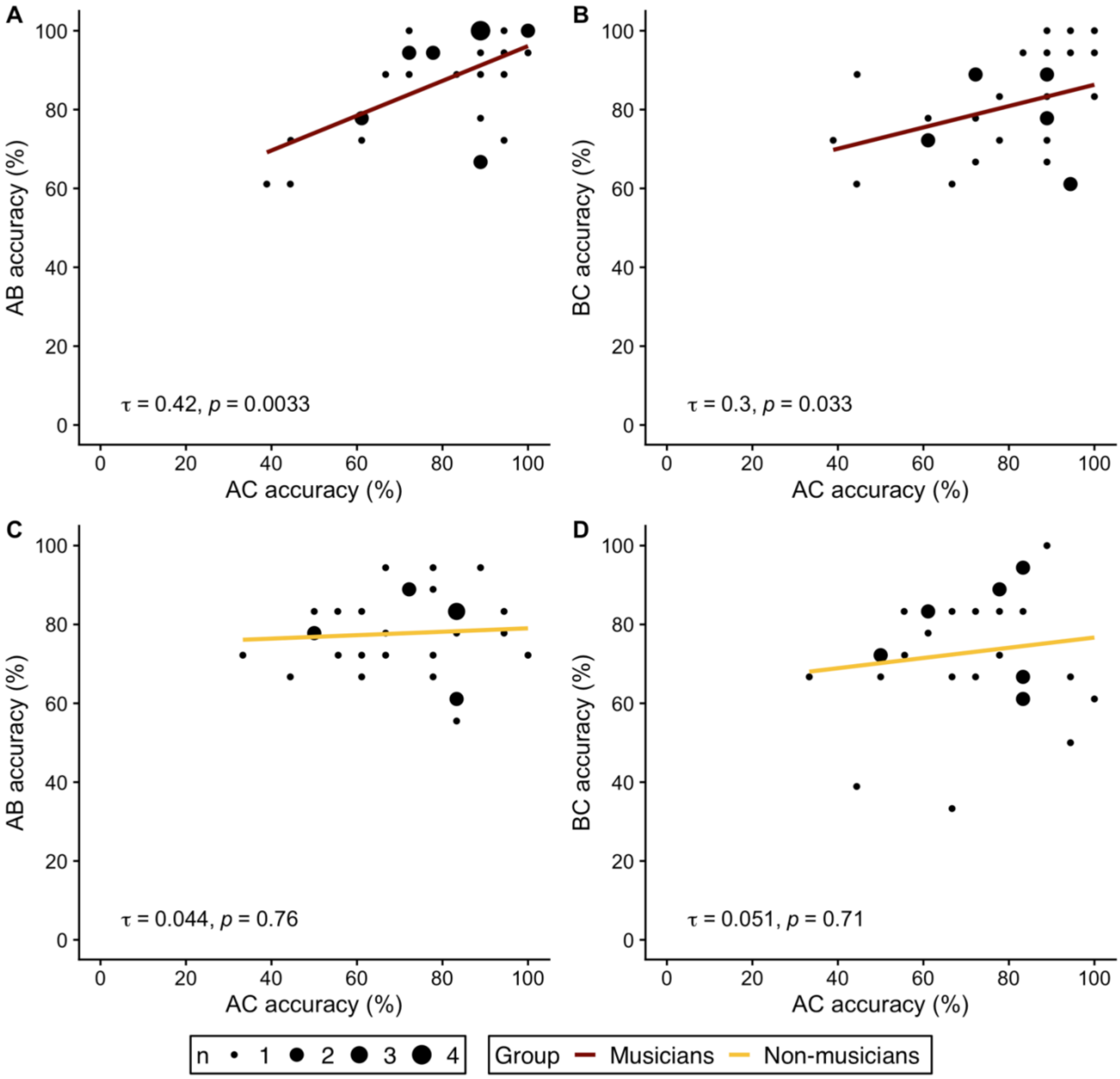

Figure 4. Correlations of accuracy in indirect AC-trials (x-axes) with accuracy in direct AB- and BC-trials (y-axes). (A) Correlation of accuracy in indirect AC-trials and direct AB-trials in musicians. (B) Correlation of accuracy in indirect AC-trials and direct BC-trials in musicians. (C) Correlation of accuracy in indirect AC-trials and direct AB-trials in non-musicians. (D) Correlation of accuracy in indirect AC-trials and direct BC-trials in non-musicians. Kendall's τ are reported as correlation coefficient. Dot sizes indicate the frequency of identical values. Figure from Hoffmann et al. (2022b).

2.2 Study 2: Influence of musician's dystonia and musical activity on temporal discrimination thresholds[2]

2.2.1 Methods

Participants:

The final sample consisted of three groups: (i) patients with focal musician's dystonia (MD) of the hand (n = 20), (ii) healthy musicians (n = 20) and (iii) healthy non-musicians (n = 20). Participants of the three groups were matched for age and gender. Healthy musicians and musicians with MD were furthermore matched by instrument. Excluded were patients and healthy control participants who reported a history of psychiatric disorders, cognitive impairment, visual field defects and decreased visual acuity that could not be corrected to normal. Healthy musicians and non-musicians were furthermore screened for dystonia or further movement disorders. Detailed characteristics of patients and healthy control participants are displayed in Table 1 in Borngräber et al. (2022).

Assessment of TDT:

TDTs were assessed in three modalities (visual, tactile, visual-tactile) using a previously described paradigm (Bradley et al., 2009). In the visual modality (VV), two flashlights were presented to the participants in the peripheral visual field. For the tactile modality (TT), two electrical stimuli were administered to the participants, one at the index and one at the middle finger. Electrical stimuli were non-painful, and the stimulation intensity was set to the doubled individual sensory perception threshold. For the mixed visual-tactile (VT) modality, one visual (i.e. flashlight) and one tactile (i.e. electrical impulse) were presented to the participants. Pairs of stimuli were presented every 5 s. The first pair of stimuli was administered synchronously. In the subsequent pairs, the time interval between the two stimuli increased in steps of 5 ms. Participants were asked to indicate verbally whether they perceived the two stimuli as synchronous or asynchronous. The run was terminated when participants reported three consecutive pairs to be asynchronous. The first value was then defined as the respective TDT. Per body side (left, right) and modality (visual, tactile, visual-tactile), TDT measurement was repeated four times with varied order of

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[2] Parts of this section are adapted from Borngräber, F.*, Hoffmann, M.*, Paulus, T., Junker, J., Bäumer, T., Altenmüller, E., Kühn, A. A., & Schmidt, A. (2022). Characterizing the temporal discrimination threshold in musician's dystonia. *Scientific reports*, *12*(1), 14939. CC-BY 4.0.

modality and body side for each participant. The median of the four repetitions per modality and body side was calculated.

In addition, TDTs of dystonic and non-dystonic hands and fingers were compared in the MD patient group. All three modalities (visual, tactile, visual-tactile) were compared between dystonic and non-dystonic hands. For comparison of dystonic and non-dystonic fingers, tactile and visual-tactile modalities were included. Further details of TDT measurement are described in Borngräber et al. (2022).

Additional measures:

A further aim of the study was the investigation of factors that potentially influence the TDT, such as musical activity, disease variables and personality profiles. Musical activity was assessed in healthy musicians and patients with MD and comprised information on the age of first instrumental practice, total years of instrument playing and the accumulated practice time. Further information on all three potentially influencing factors can be found in Borngräber et al. (2022).

Statistical analysis:

TDTs were analyzed as dependent variable and compared between groups and modalities. To this end, classical null hypothesis testing was combined with Bayesian analyses as described in Borngräber et al. (2022): For null hypothesis testing, non-parametric analyses were conducted using R (version 3.6.3, R Core Team, 2020), since data was mostly non-normally distributed. For analysis of TDTs, repeated measures ANOVAs for non-normally distributed data were conducted using the R-package MANOVA.RM (Friedrich et al., 2021). Wald-type statistics (WTS) with permuted p-values were calculated. For post-hoc analyses, pairwise comparisons were conducted using the MANOVA.RM package for the within factors (modality, dystonic/non-dystonic hands, dystonic/non-dystonic fingers) and the package GFD (Friedrich et al., 2017) for comparisons between groups. In all post-hoc analyses, Bonferroni correction was applied to adjust p-values for multiple pairwise comparisons.

In addition, a Bayesian statistical approach was applied using JASP (version 0.14.1, JASP Team, 2020) with default priors. Bayesian statistics have the advantage that not only evidence against but also for the null hypotheses can be quantified (Keysers et al., 2020; van Doorn et al., 2021). Therefore, repeated measures Bayesian ANOVAs and inclusion Bayes factors (BF_{incl}) were calculated. BF_{incl} express the evidence for including a particular effect. Bayesian t-tests with uncorrected BF_{10} were calculated for post-hoc comparisons. BF_{10} indicates the probability of the data under the alternative hypotheses (H_1) compared to the null hypotheses (H_0). For interpretation of results, the strength of evidence provided by the respective BFs was classified according to common guidelines (Keysers et al., 2020; van Doorn et al., 2021).

To furthermore investigate the associations of TDTs with potentially influencing factors (i.e. musical activity variables, disease variables, personality profiles), exploratory Spearman rank correlations were calculated.

2.2.2 Results

Comparison of TDTs between groups and modalities:

In the main analyses, TDT values were compared between groups and modalities. Data analysis revealed a significant group effect supported by strong evidence for the inclusion of this effect in the Bayesian ANOVA. Post-hoc tests revealed that healthy musicians had significantly lower TDT values than healthy non-musicians, supported by strong evidence in Bayesian analyses. No differences between MD patients and healthy musicians were found. Similarly, TDTs of MD patients and healthy non-musicians did not differ. For both comparisons, however, Bayesian t-tests indicated weak evidence in support of the alternative hypothesis (i.e. group differences). Moreover, the main effect of modality was significant with strong evidence as revealed by Bayesian ANOVA. TDTs in the visual-tactile modality were significantly higher than both in the visual and tactile modality, supported by strong evidence of Bayesian analyses in both comparisons. There was no difference between TDTs in the visual and tactile condition with Bayesian t-test revealing moderate evidence for no difference. The interaction between group and modality was not significant with weak evidence for the null hypotheses (i.e. no presence of the interaction) revealed by the Bayesian ANOVA. Figure 5 displays data of the three groups and modalities. Detailed statistical results are reported in Borngräber et al. (2022).

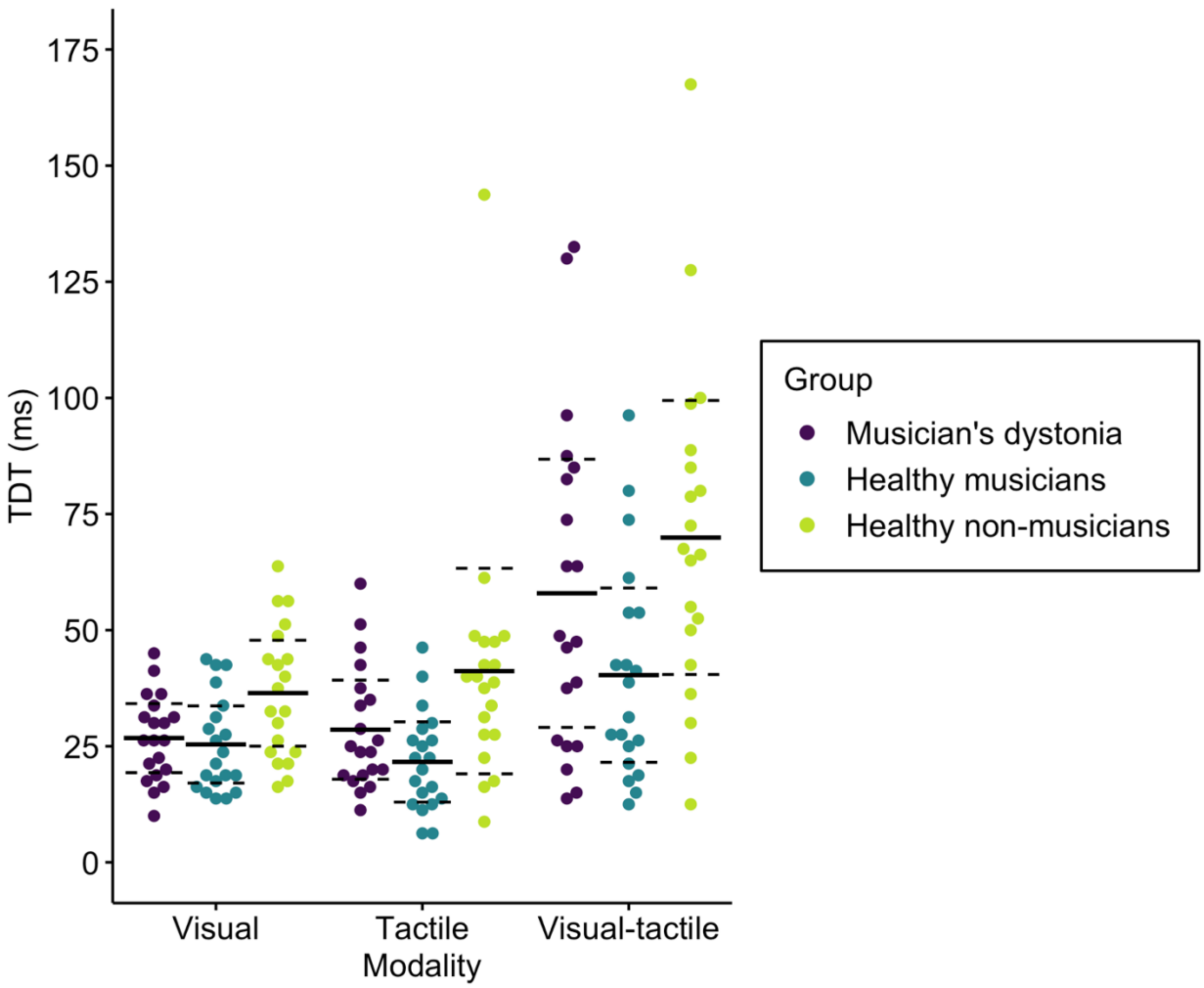

Figure 5. Temporal discrimination thresholds (TDTs) in patients with musician's dystonia (MD), healthy musicians, and healthy non-musicians. TDTs were measured in three modalities: visual (VV), tactile (TT) and visual-tactile (VT). TDT values are given in milliseconds (ms). Solid lines mark the respective mean. Dashed lines mark the 95% confidence interval of the mean. Figure adapted from Borngräber et al. (2022).

Comparison of dystonic and non-dystonic hands and fingers:

In addition, TDT values were compared between dystonic and non-dystonic hands as well as between dystonic and non-dystonic fingers in MD patients (see Figure 2 in Borngräber et al., 2022). In both analyses, the modality effect was significant and, accordingly, the Bayesian ANOVA yielded strong evidence for inclusion of the modality effect. TDTs in the visual-tactile condition were higher compared to TDTs in the tactile condition in both analyses. In the comparison of dystonic and non-dystonic hands, post-hoc tests additionally revealed higher visual-tactile than visual TDTs, whereas there was no difference between visual and tactile TDTs. There were no differences between dystonic and non-dystonic hands or dystonic and non-dystonic fingers, supported by moderate evidence of Bayesian analyses for the null hypotheses (i.e. no difference). The respective interaction effects of modality and hand or modality and finger were not significant in both comparisons, with weak evidence for the null hypotheses (i.e. no presence of the interaction) revealed by the Bayesian ANOVA. Detailed statistical results are reported in Borngräber et al. (2022).

Correlations with potentially influencing factors:

Exploratory correlations of TDT with potentially influencing factors (i.e. musical activity variables, disease variables and personality profiles) were calculated. In healthy musicians, a positive correlation between age of first instrumental practice and visual-tactile TDTs was found, indicating that an earlier start of instrumental practice is related to lower visual-tactile TDT scores. On the contrary, higher visual-tactile TDTs were related to an earlier age of first instrumental practice in the group of MD patients, although this correlation did not reach the significance level of $p < 0.05$. In MD patients, higher accumulated practice time is also associated with lower visual TDT, although not reaching significance. Both in MD patients and healthy musicians, no further correlations between musical activity variables and TDTs were found. Similarly, no significant correlations between TDTs and disease-related variables or personality profiles were observed in MD patients. Detailed results of the correlation analyses are described in Table 2 in Borngräber et al. (2022).

3. Discussion

The discussion is split according to the two studies that form the basis of this dissertation. Results of study 1 are discussed and interpreted in section 3.1 and results of study 2 in section 3.2. For both studies, limitations and future research directions are described.

3.1 Study 1: Influence of musical activity on visual-melodic memory integration

3.1.1 Summary and interpretation of the results[1]

The aim of study 1 was to investigate whether there is an influence of musicianship on memory integration of musical and visual information. The ability of professional musicians and non-musicians to associate melodies with visual objects and how the two groups form integrated representations of melodic-visual stimuli were studied using an associative inference paradigm. To this end, accuracy and RTs were compared between professional musicians and non-musicians in direct (i.e. associations of melodies and visual objects) and indirect trials (i.e. associations of two objects that were indirectly connected via a common melody; Hoffmann et al., 2022a, 2022b).

As described in Hoffmann et al. (2022b) the results showed that musicians as well as non-musicians performed above chance level in direct and indirect trials, indicating that both musically trained and untrained participants efficiently used melodies to build associations with visual information. Importantly, musicians and non-musicians did not only reliably learn associations between melodies and objects but could also form integrated representations of two objects that were not experienced together but linked via a common melody. Furthermore, results revealed that musicians had a higher performance in both trial types compared to non-musicians. This is not surprising given that musicians have been shown to have superior auditory memory, whereas visual memory seems to be comparable between musicians and non-musicians (Cohen et al., 2011). Similarly, more recent studies also revealed that musicians can have superior memory performance, although this advantage is modulated by the type of stimuli with a better performance in domains that are trained by the musical activity (Talamini et al.,

[1] Parts of this section are adapted from the published manuscript (Hoffmann, M., Schmidt, A.*, & Ploner, C. J.* (2022). Musical expertise shapes visual-melodic memory integration. *Frontiers in Psychology, 13,* 1-13. CC-BY 4.0) and the corresponding preprint (Hoffmann, M., Schmidt, A.*, & Ploner, C. J.* (2022). Musical expertise shapes visual-melodic memory integration. bioRxiv.)

2017, 2021). It seems reasonable to conclude that superior auditory memory abilities also contributed to the better performance in musicians in the present study (Hoffmann et al., 2022b). It seems less likely that performance differences were due to a general better memory in musicians, although this cannot be completely ruled out by the design used in the study.

To succeed in correctly answering AC-trials, A- and C-stimuli that were never perceived together must be connected via the B-stimulus at some point between the encoding and retrieval phase. Two processes that describe how and when memory integration may occur have been identified within the research field of memory integration and inferential reasoning (Duncan & Schlichting, 2018; Pajkert et al., 2017; Shohamy & Daw, 2015; Zeithamova, Schlichting, et al., 2012; Zeithamova & Preston, 2010): The first process is termed integrative encoding and refers to the formation of ABC-triplets already during encoding by reactivating AB-pairs when encountering related BC-pairs resulting in shorter response times at the time of AC-decision (Duncan & Schlichting, 2018; Shohamy & Wagner, 2008; Zeithamova, Schlichting, et al., 2012; Zeithamova & Preston, 2010). The second process has been named recombination at retrieval and describes that the underlying AB- and BC-associations are separately stored in memory and subsequently retrieved and newly combined at the time of AC-decision resulting in more flexible but slower cognitive operations (Shohamy & Daw, 2015; Zeithamova, Schlichting, et al., 2012).

The results of the current study also align with these documented strategies. Similar to previous studies (Pajkert et al., 2017; Schlichting et al., 2014; Shing et al., 2019), analyses of RTs and correlations led to the conclusion that musically trained and untrained individuals used different strategies for memory integration of musical and visual information (Hoffmann et al., 2022a, 2022b). In the non-musician group, the shorter RTs in indirect vs. direct trials suggested that non-musicians form combined representations of related AB- and BC-associations already during the encoding when the BC-pair is presented. Thus, non-musicians memorize an integrated ABC-triplet (i.e. memory of object-melody-object triplet), enabling them to retrieve the AC-association faster during the retrieval phase, since the ABC-triplet is already available. In line with this assumption, there were no correlations between accuracy in AC-trials and accuracy in AB- or BC-trials, indicating that decisions in AC-trials are less dependent on correct knowledge of the underlying AB- and BC-trial. This pattern was observed in non-musicians and seems to indicate a mainly integrative encoding strategy. Since non-musicians have lesser practice in actively recalling, reproducing and maintaining melodies, this strategy might help them to solve the task and memorize a complex cross-modal memory representation. It therefore seems possible that integrative encoding might represent a default mechanism for integration of visual and melodic information that is available to musically untrained persons. This strategy seems to be a more passive and recognition-based mechanism that supports the intuitive attachment of sounds to objects with no or little effort (Hoffmann et al., 2022a, 2022b).

As described in Hoffmann et al. (2022b), RTs in indirect and direct trials did not differ in the musicians group. This suggests that musicians separately memorized AB- and BC-trials, retrieved them from memory and flexibly recombined them at the timepoint of answering AC-trials. The correlation analysis corroborates this assumption revealing significant relationships of AC-accuracy with both performance in AB- and BC-pairs. Thus, these correlations might also indicate that musicians rather relied on memory of underlying AB- and BC-associations when answering AC-trials. It seems plausible that this differential strategy usage is shaped by musical training and the demands and characteristics that come with it. Musicians often memorize, recognize, recall and replay different melodies. Importantly, they do not only passively listen to music, but are trained to process and learn melodies actively and consciously. Thus, musical information plays an important role in the everyday life of musicians. It has been suggested that musicians might also have access to active learning strategies which are honed by musical training (Talamini et al., 2017). One such active learning strategy is chunking, i.e. segmenting a melody or piece into short, meaningful sections which are then memorized. Similarly, musicians might have applied such a strategy when they memorized the underlying AB- and BC-pairs that formed an ABC-triplet. This probably allowed them to form associations between melodies and non-musical information more flexibly and deliberately. Musicians therefore seem to have access not only to the default integrative encoding strategy, but also to a complimentary recombination at retrieval strategy for memory integration of visual and melodic stimuli. The recombination at retrieval strategy seems to be a rather active and recall-based strategy depending on musical training and the expertise to discriminate and memorize musical stimuli across extended periods (Hoffmann et al., 2022a, 2022b).

To summarize, two main behavioral changes in musicians were documented in the study that are likely the consequence of long-standing musical training and show that musicianship does have an influence on memory integration of musical and visual information. First, the results indicate that musicians might have a better memory performance. This memory advantage probably is constricted to the auditory domain, although no clearcut conclusions can be made about the domain-specificity. Beyond this better memory performance, the results also suggest a strategic difference between musicians and non-musicians in visual-melodic memory integration. Several implications can be derived from these results. It seems that functional and structural brain changes in musicians, that have been documented in numerous studies, are paralleled by qualitative differences compared to non-musicians. Similar qualitative strategic differences might have been present in previous studies investigating the impact of musical training on memory or other cognitive domains and might be one explanation for contradictory results in previous studies. Along with the structural and functional brain changes, the additional and more flexible cognitive strategy musicians are equipped with might also support the acquisition of new musical and non-musical cognitive skills (Altenmüller & Furuya, 2016; Benz et al., 2016; Herholz & Zatorre, 2012; Schlaug, 2015). It even has been suggested that musician's access to multiple and alternative strategies might be one explanation why musical training and the associated brain changes might have a beneficial effect for the cognitive outcome in musicians following brain damage (Omigie & Samson, 2014). Whether the strategies identified in the present study also support visual-melodic memory integration in elderly or cognitively impaired individuals needs to be addressed in future studies.

3.1.2 Limitations

The study has limitations. As described in Hoffmann et al. (2022b), the main limitation is the choice of the melodic stimuli used in the study. The melodic stimuli have been carefully evaluated for recognition in a pilot experiment with participants differing in their levels of musical activity. Based on this pilot experiment, the melodies were included or excluded in the final stimuli set. In addition, only a small number of participants of the main experiment reported to recognize one or two of the presented melodies. However, the possibility remains that musicians had a feeling of familiarity for some of the included melodies. Musicians most probably know more musical pieces than non-musicians since they work with different melodies regularly when practicing and playing their instrument.

Earlier research has also shown that musicians do not only judge more melodies to be familiar but also are faster in their familiarity decision compared to non-musicians (Gagnepain et al., 2017). It has also been proposed that familiar melodies can be associated with specific contextual memories to a higher degree in musicians than non-musicians (Groussard, La Joie, et al., 2010). These findings suggest that in the present study similar mechanisms might have contributed to a higher rate of correct answers in the musician group. However, this does not argue against the interpretation that musicians mainly use a recombination at retrieval strategy for memory integration (Hoffmann et al., 2022b).

Another limitation is that no condition with solely visual stimuli was administered. Previous research has shown that musicians have better memory performance especially for auditory stimuli and domains that are trained by musical activity (Talamini et al., 2017, 2021). Better performance of musicians is therefore not surprising and probably due to the superior auditory memory (Hoffmann et al., 2022b). However, it cannot be completely ruled out that group differences might depend on a general better memory performance in musicians. An experimental condition with only visual stimuli might help to further elucidate whether performance and strategy differences between musicians and non-musicians are also evident in the visual domain.

A further limitation of the study is its cross-sectional design which prevents any causal claims about the influence of musical training on melodic-visual memory integration. Longitudinal studies are scarce within the field of research on the impact of musical activity on brain and behavior. Although pre-existing differences between musicians and non-musicians might have contributed to the results, it seems plausible that the observed performance differences between musicians and non-musicians are rather due to the nature of musical training and requirements of professional musicianship. In addition, the groups of musicians and non-musicians were comparable in the main sociodemographic variables (i.e. age, sex, educational background) to minimize potential other influencing factors.

3.1.3 Future research directions[1a]

The results of the study suggest that musicians and non-musicians use different strategies for memory integration of visual and melodic information. Future studies should investigate whether these different behavioral strategies in musicians and non-musicians are also underpinned by distinct neural mechanisms (Hoffmann et al., 2022a, 2022b). Investigating underlying neural mechanisms of memory integration of visual and melodic information in musicians and non-musicians might yield insights on the following aspects: Since various functional brain changes have been documented in musicians when performing music-related tasks (Fauvel et al., 2013; Groussard, La Joie, et al., 2010; Herdener et al., 2010; Herholz & Zatorre, 2012), it is conceivable that functional brain differences between musicians and non-musicians are also evident for the visual-melodic memory integration task. For instance, it is conceivable that in musicians not only neural networks supporting recognition memory, but also areas that are involved in recall memory are activated during the task. In addition, since increased activity in motor-related brain areas has been reported in musicians even when only listening to music (Alluri et al., 2017; Bangert & Schlaug, 2006; Brattico et al., 2016), it might be possible that in musicians brain networks are activated which are also related to playing their respective musical instrument. Thus, musically trained individuals might also rely on differential brain networks during the present task which allow them to react more flexibly compared to non-musicians. In addition, performance differences might also be associated with structural brain changes induced by musical training. For instance, a previous study investigated structural brain plasticity and behavioral changes in response to musical training in children and found that structural brain changes were associated with improvements in music-related motor and auditory tasks (Hyde et al., 2009).

The findings suggest that both musically trained and untrained persons can form reliable associations of melodies and non-musical information. Thus, it seems likely that music can function as a useful mnemonic device to memorize and retrieve non-musical information. As outlined in Hoffmann et al. (2022a), the idea of music as a mnemonic device is not new and musical mnemonics have been applied in various educational contexts up to the academic level to teach complex contents, as for example health

[1a] Parts of this section are adapted from the corresponding preprint (Hoffmann, M., Schmidt, A.*, & Ploner, C. J.* (2022). Musical expertise shapes visual-melodic memory integration. bioRxiv.)

sciences (Cirigliano, 2013) or biochemistry and molecular biology (Crowther, 2012a, 2012b). Different mechanisms that might promote learning through songs have been suggested, including enhancement of recall by presenting information in a structured and organized way, reduction of stress, multi-modal learning opportunities and increased enjoyment (Crowther, 2012b; Thaut et al., 2014). It is, however, not clear whether musical mnemonics effectively enhance memory of the presented information with some studies reporting increased recall of sung versus spoken information (Kilgour et al., 2000; Knott & Thaut, 2018; Purnell-Webb & Speelman, 2008), whereas other studies did not find this memory-enhancing effect of music in healthy participants (Lehmann & Seufert, 2018; Racette & Peretz, 2007; Tamminen et al., 2017). Superior memory of sung compared to spoken information has also been found in individuals with memory impairment, including patients with multiple sclerosis (Thaut et al., 2014), Alzheimer's disease (Simmons-Stern et al., 2010) or 6 months poststroke (Leo et al., 2018). The results presented in Hoffmann et al. (2022b) and in this dissertation indicate that music could not only function as a mnemonic device for verbal but also for visual information. Future studies should address how these findings might support learning in pedagogical or therapeutical settings (Hoffmann et al., 2022a, 2022b). To this end, it might be fruitful to investigate different target groups, including healthy participants of different age groups and persons with memory impairments. Given the documented plasticity effects induced by musical training as well as the probable strategic difference of musicians in melodic memory tasks revealed by the study of this dissertation, it furthermore seems mandatory to control for musical expertise when using musical stimuli and when investigating the pedagogical or therapeutic potential of music as a mnemonic device. Previous studies investigating the potential of music as mnemonic device did rarely take the musical activity of participants into account, although it has been shown that musical training can modulate the mnemonic effect of sung and spoken information in patients with Alzheimer's disease (Baird et al., 2017).

Moreover, in the present study, the melodies were rather simple and neutrally played excerpts. As further research idea it might be interesting to systematically vary parameters of the musical stimuli and compare how these different parameters can modulate memory performance. For instance, it has been shown that memory for music and associated verbal memory can be modulated by musical reward (Ferreri & Rodriguez-Fornells, 2017), pleasantness (Cardona et al., 2020) and emotions (Aubé et al., 2013; Eschrich et al., 2008). These parameters of musical stimuli could also influence visual-melodic memory integration and some group of persons (e.g. non-musicians, clinical populations) might benefit in their memory performance from these modulators.

3.2 Study 2: Influence of musician's dystonia and musical activity on temporal discrimination thresholds

3.2.1 Summary and interpretation of results[2]

The aim of study 2 was to investigate the influence of musicianship on TDTs and to elucidate how TDTs are influenced by MD. As a secondary aim, the study addressed whether TDTs are associated with different potentially influencing factors (i.e. musical activity, disease-related variables and personality profiles). To this end, TDTs were compared between MD patients, healthy musicians and healthy non-musicians using a visual, tactile and visual-tactile paradigm (Borngräber et al., 2022).

Lower TDT values in healthy musicians were found compared to healthy non-musicians, similar to a previous study (Killian et al., 2017). This finding might be explained by effects of both behavioral and brain plasticity: long-lasting extensive musical training can induce enlargement of somatosensory and auditory cortical representation (Pantev et al., 2001), which in turn might improve auditory and visual timing abilities in musicians on the behavioral level (Rammsayer et al., 2012). In the present study, TDTs in MD patients, however, did not significantly differ from TDTs in both healthy musicians and non-musicians. This finding is in contrast to findings from a previous study, in which MD patients had more abnormal TDTs compared to healthy musicians (Killian et al., 2017). However, similar to the results presented in Borngräber et al. (2022) and this dissertation, another recent study also found TDT levels to be normal in MD patients and healthy controls (Maguire et al., 2020). The latter study additionally investigated the neural correlates of TDT using resting state functional MRI and revealed a distinct pattern of associations between TDT values and brain activation in MD patients that differed from the neural correlates found in healthy control participants. This distinct pattern in MD patients might compensate for the lost neural correlates found in healthy participants and these compensatory brain activations might have contributed to the normal TDT values on the behavioral level (Maguire et al., 2020). Similarly, activation of compensatory brain circuits might have contributed to the normal TDT levels in the MD sample of the present study, although no conclusions can be made about this hypothesis, since no

[2] Parts of this section are adapted from Borngräber, F.*, Hoffmann, M.*, Paulus, T., Junker, J., Bäumer, T., Altenmüller, E., Kühn, A. A., & Schmidt, A. (2022). Characterizing the temporal discrimination threshold in musician's dystonia. *Scientific reports*, *12*(1), 14939. CC-BY 4.0.

neuroimaging or neurophysiological methods were applied (Borngräber et al., 2022). The additional Bayesian statistics in Borngräber et al. (2022) yielded weak evidence for differences between both MD patients and healthy musicians as well as between MD patients and healthy non-musicians. With Bayes factors around 1 in both comparisons, these results can rather be interpreted as absence of evidence than evidence for differences between groups (Keysers et al., 2020). It therefore can be reasoned that the results of the present study do not allow for clear conclusions whether the distinction between MD patients and both healthy musicians and non-musicians based on their TDTs is reliable (Borngräber et al., 2022).

Previous studies on TDT often restricted TDT measurement to the visual domain since no differences between visual and tactile TDT were found and the visual-tactile TDT showed a high variability (Bradley et al., 2009, 2012). However, since it is not clear whether musical activity differently impacts visual, tactile and visual-tactile domains, a further aim was to compare the different TDT modalities in this study. In line with earlier studies (Bradley et al., 2009, 2012), TDTs in the visual-tactile domain were significantly higher and more variable compared to the uni-modal visual and tactile modalities. Furthermore, there was no interaction of group and modality. Visual and tactile temporal processing, therefore, seems not to differ in MD patients. Similarly, healthy musicians showed improved timing abilities in all modalities, indicating that musical training influences all modalities to the same degree. These findings support the utilization of uni-modal TDT tasks.

Another aspect to consider is that previous neurophysiological studies revealed disorganized finger representations (e.g. reduced distance between digit representations, overlapping of receptive fields) in the primary somatosensory cortex of patients with focal hand dystonia (Bara-Jimenez et al., 1998; Elbert et al., 1998). Therefore, additional comparisons between visual, tactile and visual-tactile TDT of the dystonic and non-dystonic hand or fingers were conducted. No differences were found for both the comparison between dystonic and non-dystonic hands as well as between dystonic and non-dystonic fingers. These results align with a recent study in which tactile space orientation did not differ between affected and unaffected body parts in patients with different forms of focal dystonia (Mainka et al., 2021). Also, a recent study did not find any evidence for abnormal finger representations in the sensorimotor cortex in a group of

MD patients, questioning the idea of a distorted finger representations as a pathophysiological correlate of MD (Sadnicka et al., 2022).

In the exploratory correlation analyses, it was found that an earlier start of instrumental practice was associated with lower visual-tactile TDT in healthy musicians. This finding is in line with previous research indicating that the age of onset of musical training modulates the influence of musical training on both brain and behavior with younger starting age having a greater influence (Herholz & Zatorre, 2012; Merrett et al., 2013; Schlaug, 2015). For instance, differences in grey and white matter structure in premotor cortex and corpus callosum were found between early- and late-trained musicians (Bailey et al., 2014; Steele et al., 2013). Additionally, musicians with an earlier start of musical training also showed a superior performance in auditory and visual rhythm synchronization tasks (Bailey & Penhune, 2010, 2012; Watanabe et al., 2007) and played piano with a higher temporal precision (Vaquero et al., 2016) than late-trained musicians. The results of the present study show that an earlier start of instrumental practice might also be associated with improved cross-modal temporal discrimination. In addition, two correlations on a trend level were found in the group of MD patients: First, higher visual-tactile TDT were associated with lower age of start of instrumental practice which might be explained by maladaptive processes resulting in overlapping receptive fields (Altenmüller & Furuya, 2016). Second, higher accumulated practice times were related to lower visual TDTs in MD patients. Timing abilities, including TDTs, might be improved by longer hours of musical training as a previous study showed that long-lasting musical activity has a positive impact both on auditory and visual timing abilities (Rammsayer et al., 2012).

In summary, the results of the study presented in Borngräber et al. (2022) and in this dissertation show that healthy musicians had lower TDT levels compared to healthy non-musicians. Visual-tactile TDTs are furthermore associated with the age of first instrumental practice in healthy musicians. Musicianship therefore seems to have an influence on temporal discrimination ability in healthy musicians. The results furthermore show that TDTs in MD patients cannot be differentiated from healthy musicians and non-musicians. In addition, TDTs in patients with MD are not influenced by musical activity, disease variables or personality profiles or differ between dystonic and non-dystonic hand and fingers. It therefore seems that TDT is rather not a reliable biomarker in MD. In both

MD patients and healthy musicians, plasticity effects might have contributed to the respective TDT levels: similar to the above mentioned previous study (Maguire et al., 2020), functional plasticity with recruitment of compensatory brain circuits might explain the normal TDT levels in the MD sample. In healthy musicians, both behavioral and neural changes resulting from long-term musical training probably improved temporal discrimination in healthy musicians.

3.2.2 Limitations

This study has several limitations. As outlined in Borngräber et al. (2022), the relatively small sample sizes of 20 participants per group might have contributed to the inconclusive results in the comparison of TDTs of MD patients with both healthy musicians and non-musicians. Furthermore, the low number of participants might have also influenced the results of the correlational analyses. Here, two correlational trends were found in the group of MD patients that did not reach significance. This could be due to a low power associated with the small sample size and the results of the correlation analyses, therefore, need to be considered as exploratory. However, increasing sample size for a rare disease such as MD is rather challenging and similar sample sizes of MD patients were examined in previous studies investigating TDTs in MD (Killian et al., 2017; Maguire et al., 2020), which also found relatively normal TDTs in MD patients. Since the non-effects might be related to the small sample size, Bayesian analyses were conducted and reported in addition to classical null hypotheses testing with the aim of quantifying evidence for the null hypotheses and better explain potential non-effects as discussed above.

A further limitation of the study is that no neuroimaging or neurophysiological techniques were applied. Thus, no conclusions can be drawn about neural mechanisms that possibly contribute to normal TDTs in MD patients, similar to a previous study that found recruitment of specific brain circuits in MD patients that probably account for behaviorally normal TDT levels (Maguire et al., 2020). Similarly, reduced TDT levels in healthy musicians could be supported by distinct neural networks, although this hypothesis remains elusive without application of neuroimaging or neurophysiological methods.

It also has to be mentioned that eleven participants in the MD patient group were under treatment with botulinum toxin when participating in the study. Thus, effects of botulinum toxin might have also influenced temporal discrimination in these patients. Correlations of the TDT scores in the three modalities with time since the last injection with Botulinum toxin were calculated, but no significant associations were found (for detailed results, see Table 2 in Borngräber et al., 2022). This is congruent with a previous study that did not find any correlation between TDT scores and time since last Botulinum toxin injection (Bradley et al., 2009). Moreover, Scontrini et al. (2011) compared sensory temporal discrimination thresholds before and one month after Botulinum toxin injection in patients with cervical dystonia and found TDTs to be unchanged at the follow-up. These results suggest that TDT are probably not influenced by Botulinum toxin (Borngräber et al., 2022).

3.2.3 Future research directions

To gain a better understanding of the neurophysiology of temporal discrimination in MD and healthy musicians, it might be fruitful to investigate if temporal discrimination processing in musicians with dystonia, healthy musicians and healthy non-musicians is supported by different neural substrates. A previous study already investigated the neural associations of TDT values with resting-state functional brain activity (Maguire et al., 2020). However, the study included a mixed healthy control group containing both healthy musicians and non-musicians and only resting-state fMRI was applied, meaning that participants did not perform the TDT task within the MRI scanner. Investigating the temporal discrimination task using further neurophysiological or neuroimaging techniques (e.g. task-based fMRI, EEG) could help to better understand the neurophysiology of MD. When investigating neural substrates of TDT, it is especially important to include both healthy musicians and healthy non-musicians as separate control groups, since both structural and functional plasticity might influence the neural networks of TDT in healthy musicians and possibly also in patients with MD.

As outlined in the introduction, the identification of biomarkers can help to improve diagnosis as well as understanding of pathophysiology, genetic and environmental influences (Pirio Richardson et al., 2017; Smit et al., 2021)**.** The results of the present study further show that the TDT seems not to function as a reliable biomarker of impaired sensory processing and therefore should not be applied in clinical assessment of MD patients and healthy family members (Borngräber et al., 2022). Thus, the identification of a reliable biomarker in MD remains an important goal for future research. As potential biomarkers, different neurophysiological and neuroimaging markers have been suggested for other forms of dystonia (Smit et al., 2021) and a recent study identified an accurate neural network biomarker in patients with different forms of isolated dystonia based on structural brain MRIs (Valeriani & Simonyan, 2020). Whether these biomarkers are also suitable for the musician's dystonia type, however, still needs to be addressed in future studies.

4. Conclusion

The aim of this dissertation was to answer two open questions and investigate how musical activity influences two basic cognitive processes (i.e. memory integration of musical and visual information, temporal discrimination) on a behavioral level. To conclude, this dissertation shows that intense musical activity can influence both memory integration of visual-melodic information and temporal discrimination thresholds.

The results of the first study show that musicians seem to have an additional cognitive strategy for integration of visual-melodic information. Thus, intense musical activity can have positive consequences on memory functions, allowing musicians to use melodies more actively for retrieval of visual information and equipping them with a more flexible cognitive strategy. As shown in the second study, musical expertise furthermore shapes temporal discrimination abilities and significantly reduces temporal discrimination thresholds irrespective of the sensory modality. Improved temporal discrimination thresholds are beneficial, if not necessary, for professional musicians who mostly must react and play with high temporal precision when performing music. However, intense musical activity can also be associated with negative consequences as in the case of MD. Interestingly, temporal discrimination thresholds were not elevated in patients with MD, indicating that they are not impaired in their perceptual temporal discrimination abilities. Beyond any potential positive or negative consequences of musical activity, it should always be kept in mind that making music is first and foremost an activity of joy and creativity which should always be in balance with the high demands that often prevail in the professional music scene.

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Eidesstattliche Versicherung

„Ich, Martina Hoffmann, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Behavioral consequences of brain plasticity in musicians – Effects of musicianship on memory integration and temporal discrimination” / “Behaviorale Konsequenzen der Plastizität des Gehirns bei Musizierenden – Auswirkungen des Musizierens auf Gedächtnisintegration und zeitliche Diskrimination“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
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Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

Anteilserklärung an den erfolgten Publikationen

Martina Hoffmann hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Hoffmann, M., Schmidt, A.*, & Ploner, C. J.* Musical expertise shapes visual-melodic memory integration. Frontiers in Psychology, 2022, 13:973164.
* These authors contributed equally.

Beitrag im Einzelnen:

Das Design und die Konzeptionalisierung der Studie habe ich gemeinsam mit den Ko-Autoren festgelegt. Ich war an der Programmierung des Verhaltensexperiments sowie der Auswahl und Zusammenstellung eines Teils der musikalischen Stimuli beteiligt. In der Phase der Studienkonzeption war ich weiterhin verantwortlich für die Auswahl, Festlegung und Zusammenstellung weiterer zu erhebender Variablen und Studienunterlagen in Rücksprache mit den Ko-Autoren. Weiterhin habe ich für die Vorbereitung der Studie Literatur recherchiert sowie den Ethikantrag und die dazu erforderlichen Dokumente (u.a. Studieninformation, Einwilligungserklärung, Datenschutzerklärung) erstellt.

In der Phase der Studiendurchführung habe ich sämtliche Proband*innen selbstständig rekrutiert. Die Datenerhebung wurde vollständig von mir durchgeführt und ich war für das Datenmanagement verantwortlich.

Weiterhin habe ich die statistische Datenanalyse zu verantworten. Hierzu wertete ich die Daten mithilfe des Programms R aus. Die Skripte hierzu habe ich selbst geschrieben. Alle Tabellen und Grafiken in der Publikation sind aus diesen Skripten entstanden und wurden von mir selbst erstellt. Die Ergebnisse wurden in regelmäßigen Abständen mit den Ko-Autoren gemeinsam interpretiert und diskutiert.

Ich habe einen Erstentwurf des Manuskripts verfasst, der von den Ko-Autoren überarbeitet und ergänzt wurde. Weiterhin wirkte ich maßgeblich an der Revision und Beantwortung der Gutachterkommentare im Reviewprozess mit. Hierbei war ich insbesondere für die Einarbeitung und Beantwortung der Gutachterkommentare in Methoden und Ergebnissen zuständig.

Publikation 2: Borngräber, F., Hoffmann, M., Paulus, T., Junker, J., Bäumer, T., Altenmüller, E., Kühn, A. A., & Schmidt, A. Characterizing the temporal discrimination threshold in musician's dystonia. Scientific reports, 2022, 12(1), 14939.
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Beitrag im Einzelnen:

Im Rahmen der Studie war ich mitverantwortlich für die Rekrutierung der Proband*innen in allen drei Gruppen. Weiterhin habe ich die Daten von einem Teil der Stichprobe selbstständig erhoben.

Ich war mitverantwortlich für das Datenmanagement, die Dateneingabe und Datenaufbereitung. Da es sich bei den Daten um kleine Stichproben und nicht-normalverteilte Daten handelte, nahmen wir initial die statistische Beratung des Instituts für Biometrie und klinische Epidemiologie wahr. Die statistische Datenanalyse führte ich im Anschluss selbstständig mit den Programmen R und JASP durch. Die Skripte hierzu habe ich selbst entwickelt. Alle Tabellen und Grafiken in der Publikation sind aus diesen Skripten entstanden und wurden von mir selbst erstellt. Die Interpretation der Daten und Ergebnisse erfolgte gemeinsam mit den Friederike Borngräber, Alexander Schmidt und den weiteren Ko-Autoren.

Beim Schreiben des Manuskripts war ich für das Verfassen des Methoden- und Ergebnisteils verantwortlich. Hierbei wurde ich durch Feedback von Friederike Borngräber unterstützt. Ebenso floss mein Feedback in die Einleitung und Diskussion des Manuskripts ein. Alle Ko-Autoren konnten zur Erstfassung des Manuskripts Feedback geben. Die Revision des Manuskripts erfolgte in Zusammenarbeit mit Friederike Borngräber. Hierbei war ich für die Einarbeitung und Beantwortung der Gutachterkommentare in Methoden und Ergebnissen zuständig.

Unterschrift, Datum und Stempel des/der erstbetreuenden Hochschullehrers/in

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Druckexemplar Publikation 1

Publikation 1: Hoffmann, M., Schmidt, A.*, & Ploner, C. J.* (2022). Musical expertise shapes visual-melodic memory integration. *Frontiers in Psychology, 13,* 1-13. https://doi.org/10.3389/fpsyg.2022.973164

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Musical expertise shapes visual-melodic memory integration

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Music can act as a mnemonic device that can elicit multiple memories. How musical and non-musical information integrate into complex cross-modal memory representations has however rarely been investigated. Here, we studied the ability of human subjects to associate visual objects with melodies. Musical laypersons and professional musicians performed an associative inference task that tested the ability to form and memorize paired associations between objects and melodies ("direct trials") and to integrate these pairs into more complex representations where melodies are linked with two objects across trials ("indirect trials"). We further investigated whether and how musical expertise modulates these two processes. We analyzed accuracy and reaction times (RTs) of direct and indirect trials in both groups. We reasoned that the musical and cross-modal memory demands of musicianship might modulate performance in the task and might thus reveal mechanisms that underlie the association and integration of visual information with musical information. Although musicians showed a higher overall memory accuracy, non-musicians' accuracy was well above chance level in both trial types, thus indicating a significant ability to associate and integrate musical with visual information even in musically untrained subjects. However, non-musicians showed shorter RTs in indirect compared to direct trials, whereas the reverse pattern was found in musicians. Moreover, accuracy of direct and indirect trials correlated significantly in musicians but not in non-musicians. Consistent with previous accounts of visual associative memory, we interpret these findings as suggestive of at least two complimentary mechanisms that contribute to visual-melodic memory integration. (I) A default mechanism that mainly operates at encoding of complex visual-melodic associations and that works with surprising efficacy even in musically untrained subjects. (II) A retrieval-based mechanism that critically depends on an expert ability to maintain and discriminate visual-melodic associations across extended memory delays. Future studies may investigate how these mechanisms contribute to the everyday experience of music-evoked memories.

KEYWORDS
musical memory, visual memory, memory integration, musicianship, associative inference

Introduction

Music and memory are intimately related. Listening to specific melodies can evoke multiple memories, even in musical laypersons. Besides regulation of arousal and mood, expression of social relatedness and achievement of self-awareness, previous research identified the association of music with memories as one motivation for music listening (Laukka, 2007; Lonsdale and North, 2011; Schäfer et al., 2013). Accordingly, current theories of music processing postulate mechanisms by which music is associated with non-musical memories (Peretz and Coltheart, 2003; Koelsch, 2015; Jäncke, 2019). A modular model posits that melodic information may be stored in a musical lexicon module that may link with non-musical associative memories depending on contextual demands (Peretz and Coltheart, 2003). These memories may be episodic and may have autobiographical significance for the listener. Musical material may thereby reactivate contextual information from learning and may trigger corresponding emotional responses (Koelsch, 2015; Jäncke, 2019). Studies have moreover shown that music is particularly powerful in evoking non-musical perceptual details of previously experienced episodes (Janata et al., 2007; Belfi et al., 2016). These theories and results therefore suggest that music not only efficiently links with non-musical information, but may also integrate distinct non-musical information into complex cross-modal representations. However, how these representations are formed in the human brain has rarely been investigated. It appears possible that these representations are distinct from non-musical associative memories, as the cerebral organization of musical memory differs from other memory modalities (Groussard et al., 2010b,c; Finke et al., 2012; Esfahani-Bayerl et al., 2019).

Here, we investigated the ability of human subjects to associate visual objects with melodies and to integrate these associations into more complex representations where melodies are linked with two separately learned visual objects. We studied non-musicians as well as professional musicians. We reasoned that active musicianship might modulate the underlying memory processes, since active music making has been shown to critically depend on learning and memory (Wan and Schlaug, 2010; Brown et al., 2015; Altenmüller and Furuya, 2016). Musicians frequently learn entire musical pieces or a repertoire of tunes and know their musical structure, melodies and harmonic progressions by heart. Musical performance moreover puts particular demands on cross-modal memory abilities, as it requires an association of visual notation with sounds and corresponding motor responses (Jäncke, 2019). In line with this, music making, in particular at a professional level, has been shown to be associated with changes in brain areas that are involved in learning and memory. For instance, gray-matter volumes in the hippocampus differ between musicians and non-musicians and increase with the amount of musical expertise (Groussard et al., 2014). In addition, stronger hippocampal activation was found in musicians compared to non-musicians in a musical familiarity task which might further indicate specific memory abilities in musicians (Groussard et al., 2010a).

In our study, we used a variant of the associative inference paradigm, i.e., a task that has previously been used in behavioral and fMRI studies of visual associative memory (Preston et al., 2004; Zeithamova and Preston, 2010; Zeithamova et al., 2012a; Pajkert et al., 2017; Shing et al., 2019). This task assesses a subjects' ability to associate and memorize pairs of items (e.g., item "A" paired with item "B") that either overlap with pairs of items in other trials (e.g., item "B" also paired with item "C") or not (e.g., item "D" paired with item "E"). Importantly, it also assesses a subjects' ability to build integrated representations across related stimulus pairs (i.e., across A-B and B-C pairs), The underlying process is called memory integration (Zeithamova et al., 2012b; Schlichting and Preston, 2015). This cognitive faculty is a major prerequisite for building networks of interrelated memory items and for various non-mnemonic cognitive functions (Zeithamova et al., 2012b, 2019; Schlichting and Preston, 2015; Duncan and Schlichting, 2018). Previous studies have shown that analysis of accuracy and reaction times (RTs) of behavioral responses in associative inference tasks allows for inferences on the timing and nature of the corresponding integration process (Schlichting et al., 2014; Pajkert et al., 2017; Shing et al., 2019). In the visual-melodic variant used here, "A" and "C" stimuli were always visual objects in distinct trials that were linked by a common melodic "B" stimulus. Participants were thus required to memorize overlapping object-melody pairs and to form an integrated and more complex cross-modal representation where a melody links with visual objects across trials. We analyzed accuracy and RTs both for memory of object-melody associations *per se* (i.e., "direct trials") and for memory integration across overlapping object-melody pairs (i.e., "indirect trials"). We expected significant performance differences between groups that might reveal basic mechanisms underlying the association and integration of visual with musical information.

Materials and methods

Participants

A total of 60 participants was included in the study, 30 professional musicians and 30 non-musicians (Table 1). The professional musicians either studied at a music university or music school or had completed their studies and worked as instrumental teachers, freelance and orchestra musicians. All musicians were instrumental musicians (string instruments $n = 12$; keyboard instruments $n = 6$; woodwind instruments $n = 5$; brass instruments $n = 3$; plucking instruments $n = 4$). The non-musician group consisted of 30 participants without or with minimal extracurricular musical activity. Six of these participants reported that they had played or tried a musical instrument or had sung in a school choir for 6 months to 2.5 years. However, musical activity was abandoned at least 10 years prior to study participation. Non-musicians were recruited from staff and students of the Charité – Universitätsmedizin Berlin and from other Berlin

TABLE 1 Demographics and musical activity of the musician and non-musician groups.

	Musicians ($n = 30$)	Non-musicians ($n = 30$)	Test statistic and p value
Sex (female/male)	14/16	14/16	$\chi^2(1) = 0$, $p = 1.00$
Age (y)	25.40 ± 5.87	26.37 ± 4.78	$W = 377.5$, $p = 0.286$
Years of education (y)	15.37 ± 2.34	15.82 ± 1.66	$W = 404$, $p = 0.498$
Reasoning – LPS subtest number 3 (T Score)	61.83 ± 5.94	59.67 ± 6.81	$W = 537.5$, $p = 0.185$
MBEA Scale subtest (%)	94.89 ± 5.98	87.67 ± 7.12	$W = 727.5$, $p < 0.001$
Daily music listening[a] (h)	1.53 ± 1.17	1.89 ± 1.64	$W = 390.5$, $p = 0.501$
Concert visits[b]	27.83 ± 28.61	6.80 ± 16.25	$W = 785.5$, $p < 0.001$
Age of first instrumental practice (y)	5.67 ± 1.99	-	
Total years of instrumental practice (y)	19.05 ± 5.54	0.22 ± 0.59	
Accumulated instrumental practice time (h)	17,448 ± 9,005	14 ± 44	
General average weekly practice time[c] (h)	16.02 ± 7.62	0.22 ± 0.44	
Current average weekly practice time[d] (h)	24.05 ± 12.11	–	–
Absolute pitch (yes/no)	9/21	–	–

Values are given as means with standard deviations or as frequencies. χ^2, chi-square test; y, years; h¸ hours; W, Wilcoxon rank-sum test; LPS, Leistungsprüfsystem; MBEA, Montreal Battery of Evaluation of Amusia.
[a]Average hours of daily music listening during the last 12 months.
[b]Average number of attended concerts or music events during the last 12 months.
[c]Average practice time per week across all decades of musical activity.
[d]Average practice time per week during the last 12 months.

universities. One additional non-musician was excluded from data analysis, since her memory accuracy in direct trials was below chance level.

No participant reported a history of neurological or psychiatric diseases, hearing deficits or significant visual impairments. The musician and non-musician groups were matched for sex, age and educational level (Table 1). Both groups were comparable in terms of non-verbal intelligence as measured with a logical reasoning task (Subtest 3 of the test battery Leistungsprüfsystem LPS; Horn, 1983). The Scale Subtest of the Montreal Battery of Evaluation of Amusia (MBEA; Peretz et al., 2003) was used to screen for amusia and assess basic music perceptual abilities. Although musicians outperformed non-musicians in this test, all non-musician participants scored within the normal range. All participants gave written informed consent before participation in the study and were paid for participation. The study was approved by the local Ethics Committee of the Charité – Universitätsmedizin Berlin and was conducted in conformity with the Declaration of Helsinki. Determination of sample size was based on previous studies using associative inference paradigms (Pajkert et al., 2017; Schlichting et al., 2017; Shing et al., 2019) and on studies of musical memory of musicians and non-musicians (Groussard et al., 2010a; Gagnepain et al., 2017). A *post hoc* sensitivity analysis was conducted using G*Power 3 (Faul et al., 2007) for ANOVA analyses of accuracy and RTs (between, within and between-within interactions, respectively), which indicated that medium to large effect sizes (Cohen's $f = 0.37/\eta^2 = 0.12$) could be detected with the given $N = 60$ participants, an $\alpha = 0.05$ and a power of 0.80.

Assessment of musical activity

Indices of musical activity were assessed using a short questionnaire (MusA; Fernholz et al., 2019). This questionnaire covers both music reception (i.e., music listening, concert attendance) and active musical practice (i.e., instrument group, years of musical activity, weekly practice time). The weekly average time of musical practice was assessed for each age decade (i.e., 0–10 years, 11–20 years, 21–30 years etc.). Additionally, weekly average time of music making during the last 12 months and total years of instrumental practice were measured. The variables assessed *via* the MusA were used to calculate further indices of musical activity. The general average practice time across all decades was determined by calculating the mean of the weekly average time of playing music for each age decade. The cumulative practice time on the instrument was calculated by combining total years of instrument playing with weekly practice times. In addition, we assessed musical activity variables that were not covered by the questionnaire by using a short personal interview (age of first instrumental practice, played instruments, absolute pitch). Descriptive information of the indices of musical activity is reported in Table 1.

Visual-melodic associative inference task

Stimuli

In our task, both visual and musical stimuli were used. Visual stimuli were taken from the Bank of Standardized Stimuli (BOSS Phase II; Brodeur et al., 2014) and consisted of 331 colored images of everyday objects (e.g., tools, food, clothes, toys etc.).

Musical stimuli involved 43 melodies played in a piano voice, without orchestration and lyrics, even if the original piece included lyrics. Melodies were taken from various genres, such as classical music, jazz, folk songs (from non-German speaking countries) or themes from older TV series or movies (see Supplementary Table 1). We aimed to include melodies that are unlikely to be associated with visual information (e.g., themes from popular movies) or with autobiographical memories (e.g., children's songs, pop songs, major themes from classical music). Only melodies were included that were not on web-based lists of canonical works of classical music. Melodies had a mean duration of 7 s (Range: 5–10 s). Melodies had a different duration in order to preserve the musicality of the stimuli and avoid cutting the melody in the middle of a phrase or playing them at a much faster or slower tempo. We further verified that length of melodies did not predict accuracy in direct trials (see Supplementary Table 2).

Musical stimuli were evaluated for familiarity in a pilot experiment with $n = 19$ participants with different levels of musical training [$n = 3$ non-musicians, $n = 5$ inactive amateur musicians (age of first instrumental practice: $M = 8.00$, $SD = 1.73$, range: 6–9 years; total years of instrumental practice: $M = 7.75$, $SD = 2.06$, range: 5–10 years), $n = 4$ active amateur musicians (age of first instrumental practice: $M = 5.25$, $SD = 1.00$, range: 6–8 years; total years of instrumental practice: $M = 17.00$, $SD = 5.00$, range: 12–22 years) and $n = 7$ professional musicians (age of first instrumental practice: $M = 5.14$, $SD = 1.21$, range: 4–7 years; total years of instrumental practice: $M = 17.67$, $SD = 2.80$, range: 15–23 years)]. Three additional melodies were pre-rated, but excluded from the experiment since they had a high level of recognition (i.e., between 21 and 26% of participants recognized them). During the experiment, participants were asked to verbally report if they knew the melody. Seven musicians (23.33%) reported to recognize one or two melodies, one non-musician (3%) reported to recognize one melody.

Procedure

The experiment was performed using Presentation® software (Version 18.1, Neurobehavioral Systems, Inc. Berkeley, CA, United States) and was conducted in a quiet room. The duration of the experiment was approximately 50 min. Musical stimuli were presented *via* external speakers and participants could adapt the volume to their needs. Prior to the experiment, participants were instructed about the task with example stimuli and received a short training with a small number of trials. Melodies and objects of the training session were not included in the experiment. The experimenter repeated instructions if necessary and ensured full comprehension of instructions before the experiment was started.

The task consisted of alternating encoding and retrieval blocks. Encoding blocks were followed by an unfilled memory delay of 5 min (Figure 1A). Then, the corresponding retrieval block started. The experiment consisted of three cycles with one encoding and one retrieval block in each cycle. During the encoding blocks, participants studied pairs of objects and melodies. Some of the pairs shared a melody, i.e., objects from distinct encoding trials were paired with the same melody and were thus indirectly associated through this melody. Some of the object-melody pairs did not share a melody with another trial. During the subsequent retrieval blocks, participants were tested both for memory of the object-melody pairs ("direct trials") and for inferential associations, i.e., associations between objects that were indirectly linked *via* a common melody ("indirect trials"). Objects and melodies were unique to each cycle.

Each encoding block consisted of 18 trials with object-melody pairs. Like in previous studies with associative inference paradigms (e.g., Preston et al., 2004; Zeithamova and Preston, 2010; Pajkert et al., 2017; Shing et al., 2019) these pairs were termed AB-, BC-and DE-pairs. During each encoding block, six AB-, six BC-and six DE-trials were presented. In AB-and BC-trials, A-and C-stimuli were always objects and the B-stimulus always a melody. AB-and BC-trials were overlapping, i.e., they shared the same melody (B-stimulus) so that two distinct objects (A and C) were associated with a common melody. Participants were presented an object (A) on the computer screen and a melody (B) was played at the same time. After two to four trials, the same melody (B) was played again, but was now paired with another object (C). In addition, DE-trials were presented, consisting of one object (D-stimulus) and one melody (E-stimulus). These stimuli were non-overlapping, i.e., they did not share a melody with other trials. The combination of objects and melodies was trial-unique and pseudo-randomized for each participant. Within each encoding block, the order of the trials was pseudo-randomized using the program Mix (Van Casteren and Davis, 2006). AB-pairs were always presented before their corresponding BC-pairs, with two to four trials in between. These intervening trials were either AB-trials or BC-trials from other overlapping AB-/BC-pairs or DE-trials. DE-trials were intermixed with AB-and BC-trials and included in the design to establish a minimum distance between AB-and BC-trials and to increase uncertainty about occurrence and timing of BC-trials. Presentation time of each pair was determined by the length of the respective melody. In order to ensure that participants focused on the presented stimuli, participants were asked how they liked the melodies after each trial. Responses were given on a five-point Likert scale (1 = not at all, 5 = very much). Trials were terminated after a response was given. The inter-trial interval was 5 s.

Each retrieval block consisted of 24 trials (6 AC-, 6 AB-, 6 BC-, and 6 DE-trials). To clarify the fundamental difference between retrieval trial types, AC-trials were termed 'indirect trials' and AB-, BC-, and DE-trials were collectively termed 'direct trials' (Schlichting et al., 2014; Pajkert et al., 2017; Shing et al., 2019). In each indirect (AC-) trial, one A-stimulus (i.e., an object) was presented at the top of the screen (Figure 1B). Two C-stimuli were shown at the bottom of the screen, one representing the target object and one a foil object. Participants had to decide which of the two C-stimuli at the bottom had previously been presented with the same melody as the A-stimulus. Thus, participants had to infer which of the objects at the bottom of the screen shared an indirect relation with the object at the top *via* a common B-stimulus (i.e., a melody). Participants

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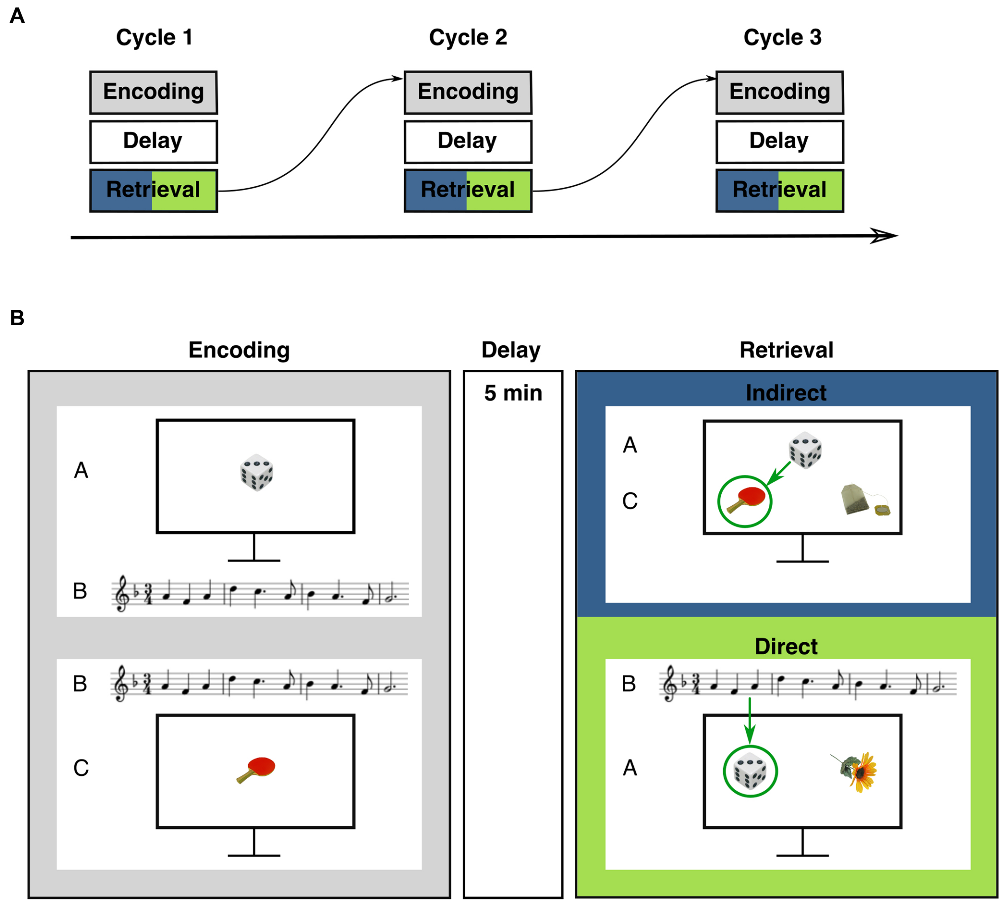

FIGURE 1
Procedure and example stimuli of the musical associative inference task. **(A)** Task structure: The experiment consisted of three alternating encoding and retrieval blocks that were separated by a delay of 5min. **(B)** Example stimuli of encoding and retrieval blocks. During the encoding block, participants studied overlapping pairs of objects and melodies (AB-/BC-pairs) and non-overlapping DE-pairs (not shown). Note the overlapping melody of AB-/BC-trials. At retrieval, participants were tested on studied direct trials (AB-, BC-, and DE-pairs) and on indirect trials (inferential AC-pairs). Green arrows indicate the correct choice.

indicated their choice *via* button press. Subsequently, memory for direct associations was tested, i.e., memory for object-melody associations as presented during encoding. All 18 AB-, BC-, and DE-stimuli of the respective cycle were tested. In these direct retrieval trials, two objects (i.e., either two A-, C-or D-stimuli) were shown in the middle of the computer screen. At the same time, a melody was played (either a B-or E-stimulus). Participants had to indicate by button press which of the two objects had previously been paired with the melody (Figure 1B).

Indirect (AC-) trials were always presented at the beginning of a retrieval block. Then, direct trials were presented (i.e., AB-, BC-, and DE-trials). This design was chosen to avoid relearning of AB-and BC-trials before testing of AC-pairs. The order both of indirect and direct trials was randomized. Presentation of the stimuli was terminated by the key press of the participants. To avoid differences in familiarity of target and foil stimuli, all foils were taken from other pairs of the same cycle. In each indirect and direct retrieval block, stimuli were always from the preceding encoding block of the same cycle.

Data analysis

Main analyses

For the musical associative inference task, we analyzed accuracy, i.e., the percentage of correct responses for each trial type, in each participant. We further analyzed reaction times (RTs) of correctly answered trials for each trial type. Medians were used to describe individual average RTs for each trial type. Due to the limited number of trials per cycle and trial type, data were averaged across cycles. Since most of the variables of interest were not normally distributed, a non-parametrical statistical approach was used throughout. Analyses were performed using R Studio (version 3.6.3; R Core Team, 2020).

First, accuracy in indirect and direct trials was compared against chance level (i.e., 50% correct answers) in both groups using a Wilcoxon signed rank test. Rank-biserial correlations (r) were calculated as measures of effect size. Then, effects of group (between-factor) and trial type (within factor) on accuracy and RTs were analyzed with a repeated measures design for non-normal data using the package MANOVA.RM (Friedrich et al., 2019, 2021). With this package, robust test statistics can be calculated, even when the basic assumptions for parametric approaches (i.e., normal distribution, equal covariances) are violated. We calculated Wald-type statistics (WTS) with permuted *p*-values to account for non-normal data distribution. Significant interactions were followed by pairwise comparisons. For post-hoc comparison of within factors (i.e., trial type), one-way repeated measure ANOVAs were performed with the RM function of the MANOVA.RM package. For post-hoc analysis of group differences, we used the package GFD (Friedrich et al., 2017) to calculate WTS combined with a permutation procedure for *p*-values. The Bonferroni-Holm correction (Holm, 1979) was used to adjust for multiple comparisons in the post-hoc analysis. As measures of effect size, partial eta squared (η^2) was calculated. Note that we calculated parametric effect sizes, since non-parametric measures of effect size for ANOVA-type analyses are currently not available. For post-hoc tests, we additionally calculated rank-biserial correlations (*r*) for non-parametric effect sizes. All effect sizes were calculated using the package effectsize (Ben-Shachar et al., 2020).

Based on previous studies using a visual associative inference paradigm (Pajkert et al., 2017; Shing et al., 2019), we analyzed correlations between accuracy in indirect and direct trial types by using Kendall's τ. For comparison of demographic data and musical activity variables across groups, Wilcoxon rank-sum tests were calculated. The significance level was set at $p < 0.05$.

Exploratory analyses

In addition to main analyses, we performed a detailed analysis of performance of related direct and indirect trials (i.e., AC-trials and their corresponding AB-and BC-trials; see 3.4.1 for detailed description) in both groups by using the rm-function of the package MANOVA.RM (Friedrich et al., 2019, 2021). As for the main ANOVA analyses, WTS with permuted *p*-values were calculated to account for non-normal data distribution. Partial eta squared (η^2) and rank-biserial correlations (*r*) were reported for effect sizes.

Results

Main analyses

Accuracy

We first analyzed differences in accuracy between direct trials with an overlapping melody (i.e., AB-and BC-trials) and non-overlapping direct trials (i.e., DE-trials) and conducted a repeated measures ANOVA for non-normal data with group (musicians, non-musicians) as between-factor and trial type as within-factor (AB-/BC-trials, DE-trials). Since the main effect of direct trial types [$WTS(1) < 1$, $p = 0.393$, $\eta 2 = 0.01$] and the interaction between group and trial type [$WTS(1) = 3.23$, $p = 0.076$, $\eta 2 = 0.05$] was not significant, all direct trials (i.e., AB-, BC-and DE-trials) were pooled for further analysis, like in previous studies (Zeithamova and Preston, 2010; Pajkert et al., 2017).

Accuracy of indirect and direct trials in both groups is shown in Figure 2. In a first step, we checked whether both groups performed above chance level (i.e., 50% correct answers) in indirect and direct trials using a Wilcoxon signed rank test. For both trial types, accuracy was significantly above chance level in musicians (indirect trials: $M = 79.44\%$, $SD = 17.08\%$, $W = 457.5$, $p < 0.001$, $r = 0.97$; direct trials: $M = 84.44\%$, $SD = 9.79\%$, $W = 465$, $p < 0.001$, $r = 1.00$) and non-musicians (indirect trials: $M = 71.29\%$, $SD = 16.38\%$, $W = 367$, $p < 0.001$, $r = 0.94$; direct trials: $M = 73.83\%$, $SD = 9.61\%$, $W = 465$, $p < 0.001$, $r = 1.00$). On an individual level, all of the included musician and non-musician participants had a performance higher than 50% in direct trials.

Accuracy was then analyzed using a repeated measures ANOVA for non-normal data with group (musicians, non-musicians) as between-factor and trial type (indirect, direct) as within-factor. There was a significant group difference [$WTS(1) = 10.49$, $p = 0.002$, $\eta^2 = 0.15$]. Averaged across trial types, musicians ($M = 81.94\%$, $SD = 12.12\%$) performed superior to non-musicians ($M = 72.56\%$, $SD = 10.25\%$). There was however no significant effect of trial type [$WTS(1) = 3.47$, $p = 0.072$, $\eta^2 = 0.06$] or interaction of trial type and group [$WTS(1) < 1$, $p = 0.545$, $\eta^2 = 0.006$]. Although musicians outperformed non-musicians in both trial types, non-musicians were apparently able to efficiently associate and memorize object-melody pairs (direct trials) and to integrate these pairs into more complex representations (indirect trials).

Reaction times

RTs of indirect and direct trials in both groups are shown in Figure 2. For analysis of RTs of correctly answered trials, a repeated measures ANOVA with group (musicians, non-musicians) as between-factor and trial type (indirect, direct) as within-factor was calculated. There was no significant main effect of group [$WTS(1) < 1$, $p = 0.623$, $\eta^2 = 0.004$] or trial type [$WTS(1) < 1$, $p = 0.828$, $\eta^2 < 0.001$], indicating that non-musicians were generally as fast as musicians in retrieving associations between objects and melodies and that RTs were not generally shorter in one of the trial types. The interaction effect of group and trial type however was significant [$WTS(1) = 7.1$, $p = 0.009$, $\eta^2 = 0.11$]. We thus compared the respective levels of the factors trial type and group (corrected for four pairwise comparisons). Post-hoc tests showed trial type differences for non-musicians [$WTS(1) = 9.34$, $p = 0.016$, $\eta^2 = 0.24$, $r = 0.54$]. RTs were significantly shorter in indirect trials ($M = 4{,}249$ ms, $SD = 1{,}526$ ms) compared to direct trials ($M = 4{,}882$ ms, $SD = 1{,}392$ ms). In the musician group, the post-hoc test did not reveal any difference between RTs in indirect ($M = 4{,}652$ ms, $SD = 2{,}276$ ms) and direct trials [$M = 4{,}118$ ms, $SD = 1{,}249$ ms; $WTS(1) = 1.917$, $p = 0.362$, $\eta^2 = 0.06$, $r = 0.20$]. Post-hoc tests between the two groups did not show significant differences for indirect [$WTS(1) < 1$, $p = 0.427$, $\eta^2 = 0.01$, $r = 0.05$] or direct trials [$WTS(1) = 5.02$, $p = 0.081$, $\eta^2 = 0.08$, $r = 0.380$] after correction for multiple comparisons.

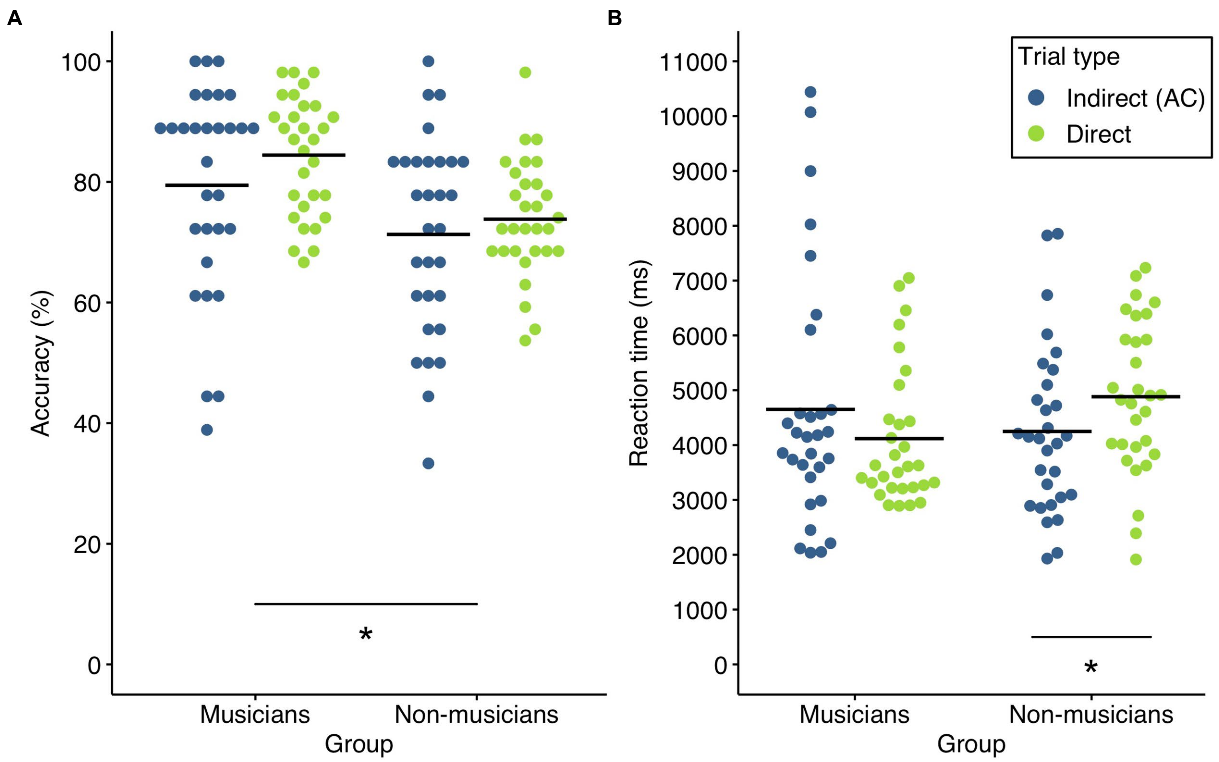

FIGURE 2
Accuracy and reaction times of both groups. **(A)** Accuracy in indirect (blue) and direct (green) trial types in musicians and non-musicians. There was a significant group effect (**p*<0.05) **(B)** Reaction times of correctly answered indirect (blue) and direct (green) trial types in musicians and non-musicians. There was a significant interaction of group × trial type. The asterisk denotes the significant pairwise comparisons (**p*<0.05 after Bonferroni-Holm correction). Solid lines represent the respective mean.

Consistent with previous studies of memory integration in healthy humans and patients with hippocampal damage (Schlichting et al., 2014; Pajkert et al., 2017; Shing et al., 2019), we reasoned that the different RT patterns might reflect different strategies for memory integration in the two groups. Shorter RTs in indirect trials compared to direct trials in the non-musician group might suggest that non-musicians build integrated and complex associations already during the encoding phase of the task. These representations may be formed as soon as an object-melody (i.e., BC) pair is encoded that shares a melody with a preceding object-melody (i.e., AB) pair. The resulting object-melody-object (ABC-) triplet may then be represented across the memory delay until the retrieval phase of the task. In this framework, the RT pattern in the musician group would suggest a distinct and more retrieval-based strategy with musicians memorizing object-melody pairs separately until the retrieval phase of task.

Correlation of accuracy between direct and indirect trials

Following the rationale of previous studies (Pajkert et al., 2017; Shing et al., 2019), we further investigated our hypothesis of distinct behavioral strategies and analyzed the correlational pattern between accuracy in indirect trials (AC) and overlapping direct trial types (AB and BC) in both groups. If musicians indeed based their AC-decisions at retrieval mainly on knowledge of separately memorized AB-and BC-pairs, a correlation between accuracy in AC-trials with accuracy of AB-and BC-trials should be expected. In non-musicians, however, no or weaker correlations should be expected, since integrated ABC-triplets may already be formed during encoding. AC-decisions at retrieval would then be less dependent on separate memory of the corresponding AB-and BC-pairs.

Figure 3 displays the correlation plots for both groups and the respective bivariate correlations. In the musician group, correlation analyses revealed significant correlations between AC accuracy and performance in the underlying direct trial types (AC-AB: $\tau = 0.42$, $p = 0.0033$; AC-BC: $\tau = 0.3$, $p = 0.033$). No correlation between AC performance and accuracy in AB-or BC-trials was observed in non-musicians (AC-AB: $\tau = 0.044$, $p = 0.76$; AC-BC: $\tau = 0.051$, $p = 0.71$). The results of the correlation analysis therefore corroborate the hypothesis of different behavioral strategies for memory integration in musicians and non-musicians.

Exploratory analyses

For a final test of the hypothesis of different strategies underlying memory integration between groups, we analyzed

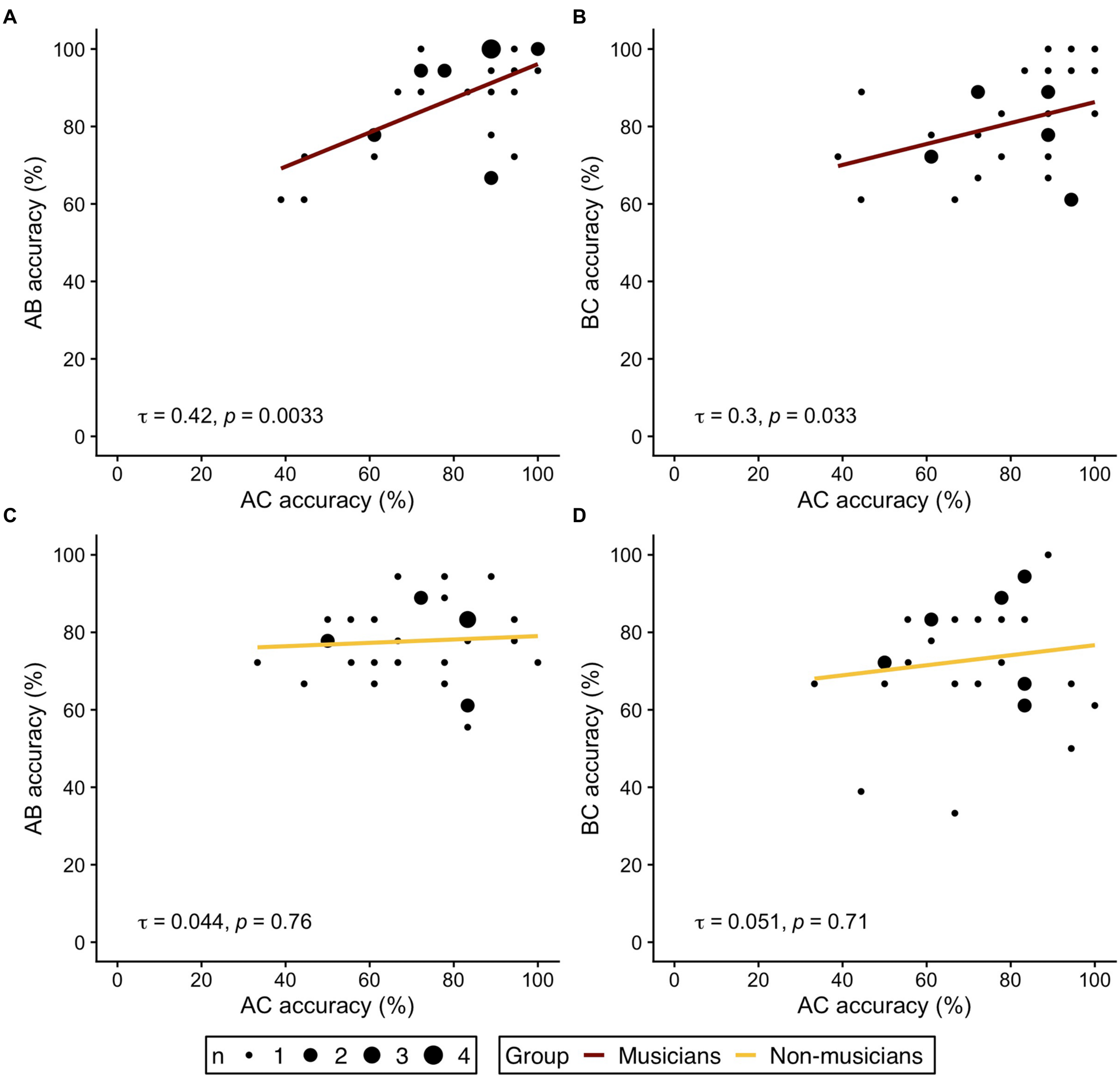

FIGURE 3
Correlations of indirect trials (AC accuracy on the respective x axis) and direct trials (AB, BC accuracy on the respective y axis) in musicians (**A,B**, red) and non-musicians (**C,D**, yellow). **(A,C)** Correlation of AC- and AB-trials. **(B,D)** Correlation of AC- and BC-trials. τ refers to the correlation coefficient from Kendall's τ. Dot size represent the number of identical values.

accuracy of the corresponding indirect and direct trials. In a first step, we took AC-trials that were correctly answered at retrieval and checked whether the corresponding AB-and BC-trials were also correct. This resulted in two response patterns: (1) Correct AC-trials, for which the corresponding AB-and BC-trials were also correct. (2) Correct AC-trials for which the corresponding AB-or BC- trials or both were incorrect. Relative percentages of these two response patterns were then calculated for each participant by dividing the number of each response pattern by the number of correctly answered AC-trials. Figure 4 displays the relative proportion of response patterns in both groups.

We then calculated a repeated measures ANOVA for non-normal data with group as between-factor and response pattern as within-factor. There was a significant main effect of response pattern [WTS(1) = 83.15, $p < 0.001$, $\eta^2 = 0.59$] and a significant interaction effect of group and response pattern [WTS(1) = 6.11, $p = 0.016$, $\eta^2 = 0.10$]. The main effect of group was not significant [WTS(1) = 1.65, $p = 0.21$, $\eta^2 = 0.03$]. Post-hoc analysis (corrected for four pairwise comparisons) revealed response pattern differences both for musicians [WTS(1) = 68.12, $p = 0.004$, $\eta^2 = 0.70$, $r = 0.94$; AB and BC correct: $M = 76.81\%$, $SD = 17.79\%$; AB and/or BC incorrect: $M = 23.19\%$, $SD = 17.79\%$] and non-musicians [WTS(1) = 21.79, $p = 0.004$, $\eta^2 = 0.43$, $r = 0.73$;

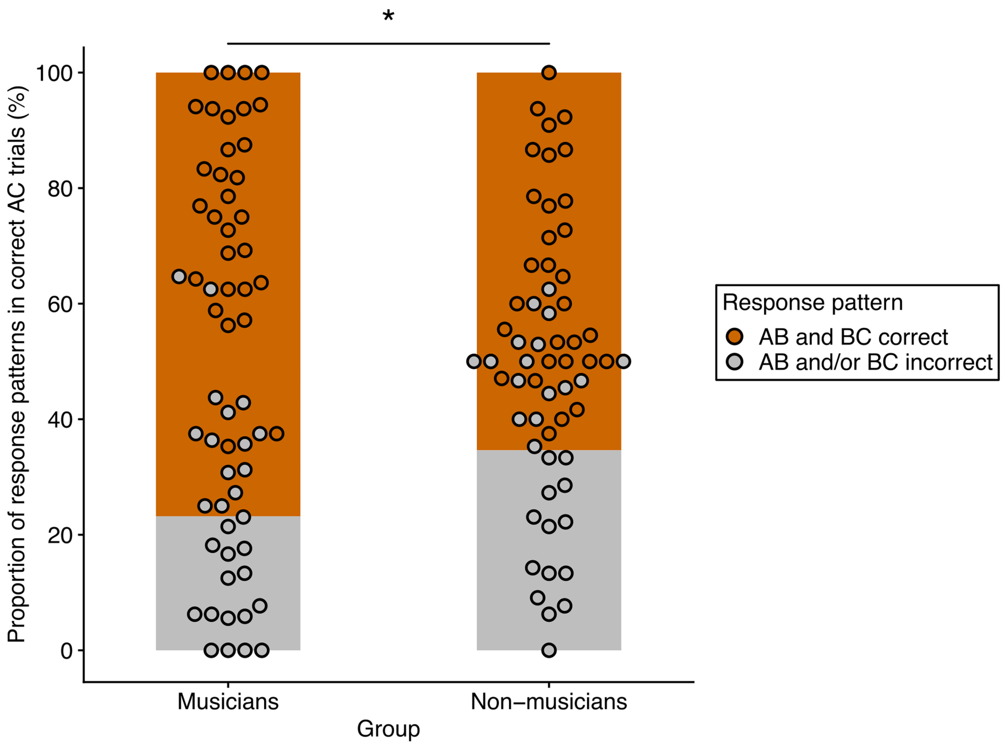

FIGURE 4
Relative frequencies of the two response patterns in musicians and non-musicians. AB and BC correct (orange) refers to the relative percentage of correctly answered AC-trials in which the corresponding AB-and BC-trials of the same overlapping ABC-triplet were also correctly answered. AB and/or BC incorrect (gray) refers to the relative percentage of correctly answered AC-trials in which the corresponding AB-or BC-or both trials of the same overlapping ABC-triplet were incorrectly answered. There was a significant effect of response patterns and a significant interaction of response pattern and group. The asterisk denotes the significant pairwise comparison of response patterns between groups (*p<0.05 after Bonferroni-Holm correction).

AB and BC correct: $M=65.37\%$, $SD=18.04\%$; AB and/or BC incorrect: $M=34.63\%$, $SD=18.04\%$]. Not surprisingly, the underlying AB-and BC-trials were correct in the majority of correctly answered AC-trials in both musicians and non-musicians. However, when we compared response patterns between groups, we found significant differences for both response patterns [AB and BC correct: WTS(1) = 6.11, $p=0.035$, $\eta^2=0.10$, $r=0.37$; musicians: $M=76.81\%$, $SD=17.79\%$; non-musicians: $M=65.37\%$, $SD=18.04\%$; AB and/or BC incorrect: WTS(1) = 6.11, $p=0.035$, $\eta^2=0.10$, $r=0.37$; musicians: $M=23.19\%$, $SD=17.79\%$; non-musicians: $M=34.63\%$, $SD=18.04\%$]. Thus, in correct AC-trials, musicians had a higher percentage of trials in which both the corresponding AB-and BC-pairs were also correct than non-musicians. Non-musicians had a higher percentage of correct AC-trials in which the corresponding AB-or BC-trials or both were incorrect. Apparently, non-musicians could still make correct AC-decisions, even in trials where they did not correctly remember the underlying AB-and BC-pairs.

Discussion

We investigated how musicians and non-musicians build associations between visual objects and melodies and integrate these associations into more complex memory representations. Using an associative inference task with visual and musical stimuli, we compared accuracy and RTs of professional musicians and non-musicians for memory of simple visual-melodic associations (direct trials) and for more complex associations in which melodies link otherwise unrelated visual object information (indirect trials). Accuracy of both musicians and non-musicians was above chance level in both trial types, indicating that participants could reliably memorize and retrieve associations of objects with melodies and were able to link distinct and previously unrelated visual information into integrated memory representations *via* association with a common melody. Although musicians outperformed non-musicians in direct and indirect trials, our results show that the process of building complex and indirect links between music and non-musical memories can happen with surprising efficacy even in musically untrained subjects. Our findings however suggest that musicians and non-musicians use different strategies for integration of visual with musical information.

Consistent with the superior overall performance of musicians in our study, musicians have been found to have superior auditory memory compared to non-musicians, not only for musical but also for non-musical auditory stimuli (Cohen et al., 2011). In both musicians and non-musicians, however, auditory memory was inferior to visual memory, which was comparable between groups (Cohen et al., 2011). Similarly, a meta-analysis found that, compared to non-musicians, musicians have a better performance in memory tasks, with a small effect for long-term memory and medium effect sizes for short-term and working memory tasks (Talamini et al., 2017). Better memory performance was however dependent on stimulus type. For short-term and working memory tasks, the memory advantage of musicians was large for tonal stimuli, moderate for verbal stimuli and small or null when visuospatial stimuli were involved. In a more recent study, visual and auditory short-term memory in musicians and non-musicians was compared using different categories of stimuli (i.e., verbal, non-verbal with contour, non-verbal without contour; Talamini et al., 2021). Stimulus sequences with contour included up and down variations based on loudness (auditory condition) or luminance (visual condition). Musicians selectively performed better in both visual and auditory contour and auditory non-contour conditions, whereas memory performance in verbal conditions was comparable. These results suggest that musical activity preferentially trains memory domains that are closely related to musical skills. In line with this, research on other fields of expertise such as chess, medicine or mental calculations suggested that experts mainly have a domain-specific memory advantage for meaningful information within their field of expertise (Ericsson and Kintsch, 1995; Ericsson, 2017). It seems therefore likely that absolute performance differences across our two groups were at least partly driven by superior auditory memory in musicians rather than by a higher overall level of memory performance.

Several influential models of musical processing postulate mechanisms that associate musical with non-musical memories (Peretz and Coltheart, 2003; Koelsch, 2015; Jäncke, 2019). One important aspect of music-evoked memories is their perceptual richness. Previous studies have shown that music-evoked memories contain more perceptual details than memories evoked by visual stimuli such as faces (Janata et al., 2007; Belfi et al., 2016). Musical information may thus be particularly powerful in binding together distinct perceptual details in integrated and complex cross-modal memory representations. One experimental approach to address this issue is the associative inference paradigm. This memory task assesses a subjects' ability to memorize pairs of items (e.g., item "A" paired with item "B") that overlap with pairs of items in other trials (e.g., item "B" also paired with item "C") presented during the encoding phase of the task. At retrieval, it assesses a subjects' ability to build integrated representations across related stimulus pairs (i.e., across AB-and BC-pairs). To correctly perform in these 'AC-trials', overlapping AB-and BC-stimuli have to be linked at some point between encoding and retrieval *via* a B-stimulus, e.g., the melody in our experiment. Two complimentary processes have been postulated that may support memory integration (Zeithamova and Preston, 2010; Zeithamova et al., 2012b; Shohamy and Daw, 2015; Pajkert et al., 2017; Duncan and Schlichting, 2018). First, memory integration may be achieved by an integrative encoding mechanism (Shohamy and Wagner, 2008; Zeithamova and Preston, 2010; Zeithamova et al., 2012b; Duncan and Schlichting, 2018). This account posits that during encoding of BC-pairs, previously studied AB-pairs become reactivated *via* the overlapping B-stimulus. Thus, integrated ABC-representations are already formed during encoding and are readily available for later AC-decisions, since the underlying AB-and BC-pairs do not have to be retrieved separately (Zeithamova and Preston, 2010). A previous study showed that response times for untrained inferential associations could be as fast as for trained direct associations, lending support to the idea that integrated memories can already be constructed during the encoding phase of associative inference tasks (Shohamy and Wagner, 2008). Second, integration of distinct but related memories can also occur during retrieval. In this case, individual AB-and BC-pairs are memorized separately and are finally recombined for AC-decisions. This process has been termed recombination at retrieval (Zeithamova et al., 2012b) and appears to be more flexible, but may result in slower responses, since additional cognitive processes are necessary by the time of retrieval that are not required for retrieval of simple AB-and BC-associations (Shohamy and Daw, 2015). Neuroimaging studies suggest that the hippocampus supports memory integration both during encoding and retrieval (Zeithamova and Preston, 2010; Schlichting et al., 2014; Tompary and Davachi, 2017; Duncan and Schlichting, 2018; van Kesteren et al., 2020; Molitor et al., 2021). In line with these neuroimaging results, patients with lesions of the hippocampus and surrounding medial temporal lobe were found to have deficits in memory integration and in making inferences between items of overlapping memory networks (Pajkert et al., 2017; Nicolás et al., 2021).

Our data suggest that musicians and non-musicians used both integrative encoding and recombination at retrieval to build complex associations between musical and visual information–albeit with distinct preferences between groups. Non-musicians showed faster responses in correct indirect (AC-) trials compared to correct direct trials. We therefore assume that non-musicians mainly used an integrative encoding strategy in which they build a melodic link between A-and C-stimuli, i.e., an ABC-triplet that is formed when the BC-pair is presented. An integrated object-melody-object representation is therefore already formed during encoding and memorized for AC-decisions at retrieval. Early integration of AB-and BC-pairs into an ABC-representation during encoding likely makes non-musicians less dependent on precise knowledge of the underlying AB-and BC-pairs. Facing the limited expertise in maintaining precise musical information across extended memory delays, this strategy may prove beneficial in non-musicians and reduce the effort in coping with the demands of the task while preserving a complex cross-modal memory representation for future decisions. We therefore suggest that integrative encoding may represent a default mechanism for integration of visual with melodic information in musical laypersons.

Other than non-musicians, professional musicians seem to base their AC-decisions more on memory of the underlying AB-and

BC-pairs, which they recombine flexibly at retrieval for AC-decisions. This may reflect that musical information has a higher relevance and is more closely related to personal behavior in professional musicians, who are often required to memorize melodies actively and consciously. For musicians, music must not only be recognized, but must also be reliably recalled and imitated. This is an important prerequisite for musical improvisation as well as for performances without sheet music. It has previously been proposed that memorizing melodies mostly involves chunking and consolidation of small musical ordered segments. Musical training may moreover foster acquisition of controlled and active learning strategies (e.g., chunking; Talamini et al., 2017). In our study, such an active learning strategy might have contributed to task performance, so that musicians could memorize and recombine the underlying chunks (i.e., pairs of melodies and objects; AB-and BC-pairs) more precisely and with less effort than non-musicians. We therefore assume that musicians not only rely on a default integrative encoding mechanism for visuo-melodic memory integration, but additionally have access to recombination at retrieval as a complimentary strategy, presumably allowing them to build associations between musical and non-musical information more deliberately and flexibly according to actual contextual demands.

Our study has important limitations. One limitation is the choice of musical stimuli. Although explicit recognition of melodies was rare in the musician group, a sense of familiarity for at least some of the melodies cannot be ruled out with certainty. This would be no surprise given that musicians have probably been exposed to a higher amount of musical material than musical laypersons. In line with this, musicians have been found to access familiar melodies more efficiently than non-musicians (Gagnepain et al., 2017). In addition, musicians are probably able to link familiar melodies to more detailed contextual and autobiographic information than non-musicians (Groussard et al., 2010a). Therefore, additional factors may have helped musicians in our study to correctly memorize and retrieve object-melody pairs. However, these factors do not argue against the use of recombination at retrieval as a predominant strategy for memory integration. A further limitation is the choice of the visual stimuli. These were simple and autobiographically irrelevant everyday objects and thus quite distinct from the complex multisensory input that usually makes up autobiographical memories. The significance of our findings for the obvious relationship of music with episodic and autobiographical memories remains therefore to be clarified.

Taken together, the findings reported here suggest that both musicians and non-musicians can associate melodies efficiently with visual information. However, musically trained and untrained individuals seem to differ in how they build integrated and more complex visuo-melodic representations. Our results suggest that integrative encoding is a default mechanism for integration of musical and non-musical stimuli that is available to a surprising degree even to musically untrained subjects. We speculate that this more passive and recognition-based mechanism may reflect a basic ability to intuitively attach sounds to objects with no or little conscious effort. We cannot be sure whether this is specific to music, but it appears possible that integrative encoding may contribute to the everyday experience of music-evoked memories. By contrast, recombination at retrieval seems to be a more active and recall-based strategy for memory integration that apparently depends on an expert ability to maintain and discriminate musical stimuli across memory delays. Future studies should investigate if distinct behavioral strategies in musicians and non-musicians depend on distinct neural substrates. Moreover, it will be important to investigate whether visual-melodic memory integration persists across extended memory delays and whether integrative encoding of melodies with new information can facilitate learning in normal subjects and subjects with memory impairments.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: Open Science Framework: https://osf.io/63mep/.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Charité – Universitätsmedizin Berlin. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MH, AS, and CP designed and conceptualized the study, analyzed and interpreted the data, drafted, reviewed, and edited the manuscript. MH collected the data. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.973164/full#supplementary-material

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Druckexemplar Publikation 2

Publikation 2: Borngräber, F.*, Hoffmann, M.*, Paulus, T., Junker, J., Bäumer, T., Altenmüller, E., Kühn, A. A., & Schmidt, A. (2022). Characterizing the temporal discrimination threshold in musician's dystonia. *Scientific reports*, *12*(1), 14939. https://doi.org/10.1038/s41598-022-18739-y

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Characterizing the temporal discrimination threshold in musician's dystonia

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The temporal discrimination threshold (TDT) has been established as a biomarker of impaired temporal processing and endophenotype in various forms of focal dystonia patients, such as cervical dystonia, writer's cramp or blepharospasm. The role of TDT in musician's dystonia (MD) in contrast is less clear with preceding studies reporting inconclusive results. We therefore compared TDT between MD patients, healthy musicians and non-musician controls using a previously described visual, tactile, and visual-tactile paradigm. Additionally, we compared TDT of the dystonic and non-dystonic hand and fingers in MD patients and further characterized the biomarker regarding its potential influencing factors, i.e. musical activity, disease variables, and personality profiles. Repeated measures ANOVA and additional Bayesian analyses revealed lower TDT in healthy musicians compared to non-musicians. However, TDTs in MD patients did not differ from both healthy musicians and non-musicians, although pairwise Bayesian t-tests indicated weak evidence for group differences in both comparisons. Analyses of dystonic and non-dystonic hands and fingers revealed no differences. While in healthy musicians, age of first instrumental practice negatively correlated with visual-tactile TDTs, TDTs in MD patients did not correlate with measures of musical activity, disease variables or personality profiles. In conclusion, TDTs in MD patients cannot reliably be distinguished from healthy musicians and non-musicians and are neither influenced by dystonic manifestation, musical activity, disease variables nor personality profiles. Unlike other isolated focal dystonias, TDT seems not to be a reliable biomarker in MD.

Musician's dystonia (MD) is an isolated, focal, and task-specific dystonia affecting up to 1–2% of professional musicians. Patients suffer from a painless muscle incoordination and/or loss of voluntary motor control while playing the instrument[1,2]. Pathophysiological findings in MD and other types of focal dystonia include reduced inhibitory mechanisms, altered sensory perception and sensorimotor integration as well as maladaptive plasticity[3]. These changes are found in multiple brain regions, e.g. basal ganglia, thalamus, midbrain, cortex and cerebellum, which is why dystonia currently is seen as a network disease[4].

Temporal aspects of somatosensory processing have drawn increasing interest as potential biomarkers in differential workup and pathophysiological understanding of movement disorders. One widely studied perceptual measurement is the temporal discrimination threshold (TDT), defined as the shortest interval at which two stimuli can be detected to be asynchronous[5]. It is a sensitive marker of aberrant sensory integration in basal ganglia and has been shown to be abnormal in different types of focal dystonia, e.g. writer's cramp[6], blepharospasm[7] and cervical dystonia[8]. A comprehensive model for the neuronal circuits involving TDT comprises that sensory stimuli (visual, sensory or auditory) access the superior colliculus, a sensorimotor structure in the dorsal midbrain, important for rapid detection of environmental stimuli and attentional orienting[9,10]. These stimuli are then

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processed through a feed forward pathway to intralaminal nuclei of the thalamus, substantia nigra and basal ganglia allowing selection of salient events for on-going behaviour[11,12].

The TDT has been proposed as a potential endophenotype (i.e. a hereditary biomarker that segregates with a disease without being symptom of it) in different forms of focal dystonia (i.e. cervical dystonia, writer's cramp, blepharospasm and spasmodic dysphonia), as 78–97% of patients[5,8,13] and 44–52% of unaffected first-degree relatives show abnormalities, suggesting an autosomal-dominant inheritance[5,8,14]. In line with this hypothesis, an enlargement of the putamen as well as reduced putaminal and superior collicular activity can be found coherent with an abnormal TDT in cervical dystonia patients and their healthy family members[5,14,15]. As up to one third of MD patients report a positive family history of autosomal-dominant inherited dystonia[16,17], extensive studies have been initiated to unravel possible genetic causes in MD families. Whereas known monogenic causes of dystonia, i.e. TOR1A, THAP1 or GNAL, have been excluded as a major cause[17–19], recent studies revealed RAB12 as a plausible candidate gene causing MD in 1.7% of patients[20], and an intronic variant in the ARSG gene increasing the risk to develop MD to a factor of 4.33[21]. But still, the far greater portion of genetic predisposition in MD remains unclear. This might be explained by reduced penetrance [i.e. a number of gene mutation carriers will remain unaffected], a phenomenon well known in focal dystonia[22]. Also, healthy non-musical family members who carry candidate genes might suffer from MD if they played an instrument on a professional level. In both cases, endophenotypes such as TDT can help detecting gene mutation carriage in unaffected family members[5].

Previous studies evaluated visual TDT measurements as a potential endophenotype in MD patients. Abnormal TDT values were found in only 20% of MD patients when healthy non-musicians were used as reference and in 45% of MD patients when compared to healthy musicians[23]. A more recent study compared MD patients (hand and larynx), focal non-musician dystonia patients (hand and larynx) and healthy controls[24]. Interestingly, TDT scores of non-musician dystonia patients differed from healthy controls, whereas MD patients did not show elevated TDT values compared to the control group. However, in this study healthy professional musicians and non-musicians were included in the control group and TDTs were only measured in the visual modality. Since timing abilities improve as a consequence of long-time musical training[25], it might be fruitful to have separate control groups for musicians and non-musicians. Additionally, it would be interesting to assess visual and tactile stimuli as patients with focal task-specific hand dystonia have proven alterations in spatial and temporal sensory discrimination[26,27].

The aim of our study was to replicate the results of earlier reports[23,24] in an independent and well-defined sample of MD patients with focal hand dystonia and evaluate the reliability of TDT as a biomarker in MD patients. To control for the above-mentioned shortcomings, we (1) added both a healthy musician and healthy non-musician control group and (2) enlarged the design by comparing visual and tactile stimulation. In addition, we compared different TDT modalities in dystonic and non-dystonic hands and fingers of patients to further characterize the biomarker regarding its global vs. local utilization as well as potentially influencing factors e.g., musical activity variables and personality profiles.

Methods

Participants. A total of 60 participants were recruited to the study, including 20 patients with focal musician's dystonia (MD) of the hand, 20 healthy professional musicians and 20 non-musician controls. Patients were recruited via the Berlin Center for Musicians' Medicine at the Charité and the Institute of Music Physiology and Musicians' Medicine at the Hanover University of Music, Drama and Media. Diagnosis of MD was established by two neurologists with expertise in movement disorders and musicians' medicine (AS, EA). Of the patients, 18 had received at least one treatment with botulinum toxin. Eleven patients were still regularly treated with botulinum toxin. For patients still treated, average time since the last botulinum injection and study participation was 11.11 weeks (standard deviation (SD) = 5.93, range: 4–20 weeks).

The first control group of healthy professional musicians was recruited from orchestras, music schools and universities in Berlin. Data of 12 individuals from the second non-musician control group have been reported previously[28]. Additional eight non-musicians were recruited from hospital staff of the Charité. All healthy participants were neurologically examined to screen for dystonia or other movement disorders. As former studies showed age- and sex-related differences of TDT scoring[5,29], both control groups were age- and sex-matched to the MD group. Healthy musicians were also matched by instrument to the MD patients.

Exclusion criteria for patients and controls were a history of other neurological diseases or psychiatric disorders, cognitive impairment, reduced visual acuity that could not be corrected to normal and visual field defects. Table 1 includes characteristics of the three groups. The study was approved by the local Ethics Board of the Charité (EA2/186/16) and conducted in conformity with the Declaration of Helsinki. All participants gave written informed consent prior to study participation.

TDT measurement. Measurement of TDT was performed as described previously[5]. TDTs were determined in three modalities: visual (VV), tactile (TT) and visual-tactile (VT). For the visual modality, pairs of flashlights were presented to participants seven degrees into the peripheral visual field. In the tactile modality, participants received pairs of non-painful electrical stimuli on the index and middle finger of one hand. Electrical stimuli were administered using square-wave stimulators (0.1 mA steps, pulse length 0.5 ms, 400 V, DS7A Digitimer; Digitimer Limited, Welwyn Garden City, UK). The individual sensory perception threshold was determined first. The stimulation intensity was doubled then and compared between fingers. In the mixed tactile-visual modality, participants received one visual and one tactile stimulus on the same body side. Stimuli were presented every 5 s. The first pair was presented synchronously; then the inter-stimulus interval increased in steps of 5 ms. Participants had to report verbally if they perceived stimuli synchronously or asynchronously. If three consecutive stimuli pairs were reported to be asynchronous, the run was terminated, and the first value taken as the dis-

Sample characteristics	Musician's dystonia patients (n=20)	Healthy musicians (n=20)	Healthy non-musicians (n=20)
Sex (male/female)	14/6	14/6	14/6
Age, years (mean ± SD)	44.25 ± 11.55	44.85 ± 12.66	43.55 ± 11.30
Instrument group			–
Woodwind instruments (n)	2	2	–
String instruments (n)	5	5	–
Brass instruments (n)	1	1	–
Plucking instruments (n)	3	3	–
Keyboard instruments (n)	8	8	–
Drums (n)	1	1	–
Age of first instrumental practice, y (mean ± SD)	7.40 ± 3.46	6.85 ± 2.72	–
Years of instrument playing, y (mean ± SD)	36.25 ± 12.20	38.00 ± 12.24	–
Accumulated practice time on the instrument, h (mean ± SD)	47,944 ± 19,298	41,479 ± 28,383	–
Age of onset of dystonia, y (mean ± SD)	34.05 ± 8.59	–	–
Duration of dystonia, y (mean ± SD)	10.45 ± 9.39	–	–

Table 1. Characteristics of patients and controls. *y* years, *h* hours, *SD* standard deviation.

crimination threshold. TDT measurement was repeated four times per modality and body side. The median of the four runs was calculated for each modality and body side. The order of the tasks varied between participants.

In 19 MD patients with unilateral focal hand dystonia (14 men, 5 women, mean age ± SD: 44.21 ± 11.86), TDTs were compared between dystonic and non-dystonic hand. All three modalities, including visual TDT, were used in this analysis. Visual TDT were classified as dystonic/non-dystonic according to the side of the affected hand (right/left).

Additionally, we compared tactile and visual-tactile TDTs of dystonic and non-dystonic fingers in 16 MD patients with a unilateral disorder affecting individual fingers (11 men, 5 women; mean age ± SD: 43.38 ± 12.94). For instance, if the index or middle finger was dystonic, then finger four and five were measured as non-dystonic finger. If finger four or five was dystonic, the measurement of index and middle finger were considered non-dystonic. None of the patients had dystonia in the thumb, so the thumb was not measured for comparing between dystonic and non-dystonic fingers. Patients with dystonia of both hands or complex unilateral dystonia affecting all fingers had been excluded in the comparison between dystonic and non-dystonic hands and fingers.

Musical activity variables. Information about musical activity were collected in MD patients and healthy musicians using structured personal interviews. We assessed the age of first instrumental practice and total years of instrument playing. In addition, we asked for weekly practice time across the age decades (i.e. until 10 years, 11–20 years, 21–30 years, 31–40 years etc.). Weekly practice time were combined with the total years of instrument playing to calculate accumulated practice time on the instrument.

Personality profiles. Personality profiles were assessed in 18 MD patients (13 men, 5 women, mean age ± SD: 45.33 ± 11.53) to investigate the association with TDT measures. The revised German version of the Neuroticism Extraversion Openness Five-Factor Inventory[30] (NEO-FFI) was used to assess personality profiles. The NEO-FFI is a self-report multidimensional personality inventory measuring five personality dimensions: neuroticism, extraversion, openness to experiences, agreeableness, and conscientiousness. Each of the dimensions is assessed by 12 items, scored on a 5-point Likert scale. Sum scores of each dimension were calculated by summing up the respective items.

Statistical analysis. TDT data are given as mean values and standard deviations. Since most of the TDT variables were not normally distributed, a non-parametrical approach was adapted throughout. TDTs were analyzed using a repeated measures design for non-normal data from the package MANOVA.RM[31], which allows to calculate robust test statistics. Wald-type statistics (WTS) combined with a permutation procedure for p-values were calculated to account for non-normally distributed data and small sample sizes. For post-hoc analysis of within factors (i.e. modality, hands, fingers) we conducted one-way repeated measure ANOVAs using the RM function of the MANOVA.RM package for pairwise comparisons of factor levels. For post-hoc comparisons of the between factor (i.e. group) we conducted pairwise comparisons of the different groups using the package GFD to calculate WTS combined with a permutation procedure for p-values[32]. Bonferroni correction was used to adjust p-values for multiple comparisons in post-hoc analysis. We additionally applied repeated measures Bayesian ANOVAs and calculated Bayes factors (BF) which allow to quantify the relative evidence that the data provide for the alternative (H_1) or null hypothesis (H_0)[33,34]. Bayesian Analyses were calculated using JASP[35] (version 0.14.1) with default priors. We calculated inclusion Bayes factors (BF_{incl}) which indicate the evidence for the inclusion of a particular effect calculated across matched models. For post-hoc analysis, pairwise comparisons using Bayesian t-tests were calculated and reported as BF_{10} and posterior odds. Posterior odds are corrected for multiple testing as implemented in JASP. BF_{10} are uncorrected and indicate the probability of the data under the H_1 compared to the H_0. A BF < 1 is considered as evidence for the null hypothesis with a BF between 1 and 1/3 indicating weak evidence, between 1/3 and 1/10 moderate evidence and a BF < 1/10 strong evidence. Accordingly, a BF > 1 is considered as evidence for the alternative hypothesis with a BF between 1 and 3 indicating weak evidence, between 3 and 10 moderate evidence and a BF > 10 strong evidence. A BF of 1 is considered no evidence for or against one hypothesis[33]. Note that we calculated parametric Bayesian ANOVAs, since non-parametric alternatives are currently not available.

To compare music activity variables between MD patients and healthy musicians, Mann–Whitney tests were calculated. Exploratory correlation analyses between TDTs, musical activity variables, clinical parameters and results of the NEO-FFI were conducted using Spearman rank correlations with 95% confidence intervals (95% CI) using the package correlation[36]. The significance level was set at $p < 0.05$. Analyses were performed using R[37] (version 3.6.3).

Results

Temporal discrimination threshold. First, a repeated measures ANOVA for non-normally distributed data with group (MD patients, healthy musicians, healthy non-musicians) as between-factor and modality (visual, tactile, visual-tactile) and body side (left, right) as within-factor was conducted. Since the main effect of body side and the interactions involving body side were not significant (see Supplementary Table S1 and Supplementary Fig. S1 in the "Supplementary Material" for detailed results), body side was not further included in the analysis. Instead, the mean of the two body sides was calculated for each modality.

Next, a repeated measures ANOVA for non-normally distributed data with modality (visual, tactile, visual-tactile, averaged across the two body sides) as within-factor and group (MD patients, healthy musicians, healthy non-musicians) as between-factor revealed a significant effect of group (WTS(2) = 13.07, p = 0.005). In line with this, the Bayesian ANOVA indicated strong evidence for the group effect (BF_{incl} = 13.29). Post-hoc analysis (with Bonferroni correction for overall 6 pairwise comparisons) did not show any differences of TDTs, averaged across the modalities, between MD patients (37.75 ms ± 16.94 ms) and healthy non-musicians (49.19 ms ± 22.84 ms; WTS(1) = 3.24, p = 0.47) as well as between MD patients and healthy musicians (29.10 ms ± 11.97 ms; WTS(1) = 3.47, p = 0.43). Pairwise Bayesian t-tests, however, revealed weak evidence for the alternative hypothesis in both comparisons (MD patients-healthy non-musicians: BF_{10} = 1.61, posterior odds = 0.94; MD patients-healthy musicians: BF_{10} = 1.41, posterior odds = 0.83). Healthy musicians had lower TDTs than healthy non-musicians (WTS(1) = 12.13, p = 0.005, BF_{10} > 100, posterior odds > 100). In addition, there was a significant effect of modality (WTS(2) = 66.89, p < 0.001) with Bayesian ANOVA also revealing strong evidence (BF_{incl} > 100). Post-hoc analysis revealed that, across the three groups, visual-tactile TDTs (56.06 ms ± 34.13 ms) were higher than both visual (29.52 ms ± 12.25 ms; WTS(1) = 48.68, p = 0.006, BF_{10} > 100, posterior odds > 100) and tactile TDTs (30.46 ms ± 20.03 ms; WTS(1) = 65.27, p = 0.006, BF_{10} > 100, posterior odds > 100). TDTs in the visual and tactile condition did not differ from each other (WTS(1) = 0.18, p = 1, BF_{10} = 0.15, posterior odds = 0.09). The interaction of group and modality did not reach significance, with the BF indicating only weak evidence for the null hypothesis, i.e. no presence of the interaction (WTS(4) = 9.22, p = 0.09, BF_{incl} = 0.44). Data of the three groups and modalities is plotted in Fig. 1.

Comparison of dystonic and non-dystonic hands and fingers. To compare TDT values between dystonic and non-dystonic hands in MD patients we calculated a repeated measures ANOVA model with modality (visual, tactile, visual-tactile) and hand (dystonic, non-dystonic) as within factors. The main effect of modality was significant (WTS(2) = 20.14, p = 0.002). In line with this, Bayesian ANOVA revealed strong evidence for the effect of modality (BF_{incl} > 100). Post-hoc analysis (with Bonferroni correction for 3 pairwise comparisons) showed that across both hands visual-tactile TDTs (54.15 ms ± 36.09 ms) were higher than TDTs in the visual (26.58 ms ± 10.88 ms; WTS(1) = 17.86, p = 0.003, BF_{10} > 100, posterior odds > 100) and in the tactile condition (28.82 ms ± 17.88 ms; WTS(1) = 20.14, p = 0.003, BF_{10} > 100, posterior odds > 100). Visual and tactile TDTs did not differ from each other (WTS(1) = 0.95, p = 1, BF_{10} = 0.26, posterior odds = 0.15). No difference between dystonic (37.72 ms ± 28.06 ms) and non-dystonic hands (35.31 ms ± 26.03 ms) was observed (WTS(1) = 0.33, p = 0.579, BF_{incl} = 0.24). The interaction of modality and hand was not significant with the BF indicating only weak evidence for no presence of the interaction (WTS(2) = 5.72, p = 0.094, BF_{incl} = 0.47).

We additionally compared TDT values between dystonic and non-dystonic fingers calculating a repeated measures ANOVA for non-normally distributed data with modality (tactile, visual-tactile) and finger (dystonic, non-dystonic) as within factors. There was a significant effect of modality (WTS(1) = 13.57, p = 0.002). Accordingly, the BF also indicated strong evidence for the inclusion of the modality effect (BF_{incl} > 100). Across the fingers, tactile TDTs (25.23 ms ± 12.04 ms) were lower than visual-tactile TDTs (56.64 ms ± 39.73 ms). There was no difference between dystonic (42.58 ms ± 31.44 ms) and non-dystonic fingers (39.30 ms ± 35.19 ms; WTS(1) = 0.46, p = 0.51, BF_{incl} = 0.28). The interaction between modality and finger was not significant with the BF indicating only weak evidence for no presence of the interaction (WTS(1) = 0.01, p = 0.93, BF_{incl} = 0.35). Results of the comparison between dystonic and non-dystonic hands and fingers are displayed in Fig. 2.

Correlation of temporal discrimination thresholds with musical activity variables. MD patients and healthy musicians did not differ in the age of first instrumental practice (Mann–Whitney test: U = 190.00, p = 0.79), accumulated practice time on the instrument (U = 148.00, p = 0.16) or years of instrument playing (U = 210.50, p = 0.78). Descriptive statistics of the three musical activity variables are reported in Table 1.

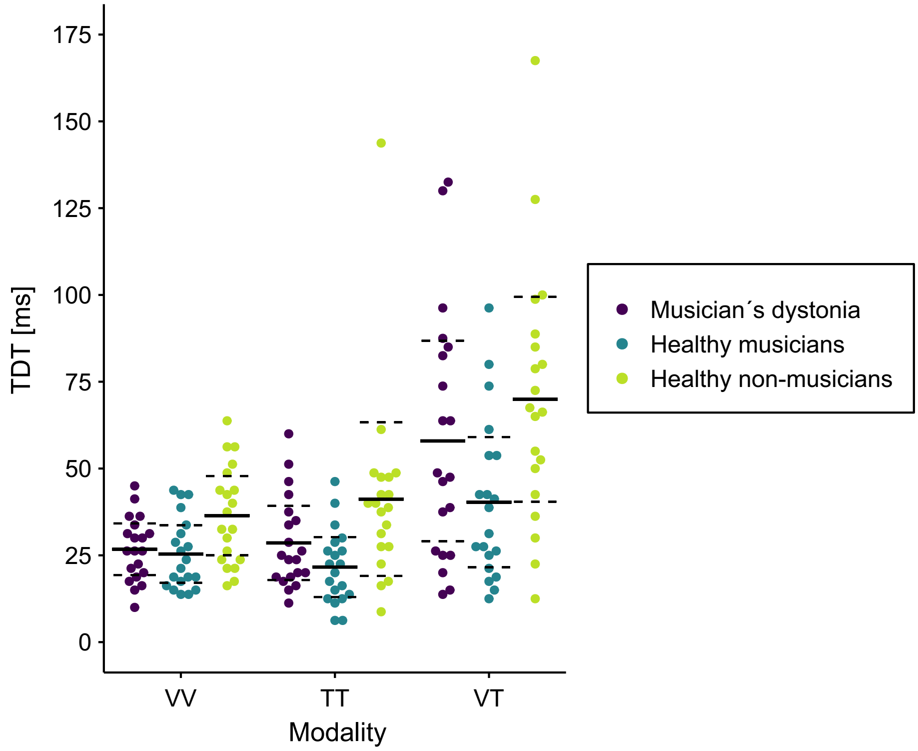

Figure 1. Visual (VV), tactile (TT) and visual-tactile (VT) temporal discrimination thresholds (TDT) in 20 patients with musician´s dystonia (purple), 20 healthy musicians (turquoise) and 20 healthy non-musicians (green). Solid lines represent the respective mean. Dashed lines indicate the 95% confidence interval of the mean.

We additionally examined relationships between TDTs and variables of musical activity. In healthy musicians, age of first instrumental practice correlated with visual-tactile TDT scores ($r_s = 0.48$, 95% CI [0.04, 0.77], $p = 0.031$), indicating that an earlier age of begin with musical training is associated with lower visual-tactile TDTs. In MD patients, however, earlier age of commencement of musical activity is associated with higher visual-tactile TDTs, although this correlation did not meet significance ($r_s = -0.4$, 95% CI [−0.72, 0.06], $p = 0.078$). Additionally, higher accumulated practice time is related to lower visual TDT in the patient group, although this correlation did not reach the significance level ($r_s - 0.41$, 95% CI [−0.73, 0.05], $p = 0.073$). No correlation between accumulated practice time and TDT scores was observed in healthy musicians. Years of instrument playing was not associated with any of the TDT scores in both groups (see Table 2 for detailed results).

Correlations of temporal discrimination thresholds and disease-related variables. In MD patients, there were no correlations between disease duration and age of disease onset and any of the TDT measures. In 11 patients who were still treated with botulinum toxin at the time of study participation, average time since the last treatment did not correlate with the three TDT scores (see Table 2 for detailed results).

Correlations of temporal discrimination thresholds with personality profiles. We additionally explored relationships of TDT scores with NEO-FFI results in 18 patients with MD. Correlation analysis did not show any significant correlations between any of the three TDT modalities and the five NEO-FFI sum scores, respectively (see Table 2 for results of the correlation analysis and Supplementary Table S2 for descriptive data of the NEO-FFI).

Discussion

In line with previous observations[23] healthy musicians had lower TDTs than non-musician controls, which, on an anatomical level can be explained by an enlargement of somatosensory and auditory representations due to long-lasting, extensive musical training[38], resulting in better timing abilities irrespective of the sensory modality[25]. In contrast to the former study[23], TDT values of our MD patients were not significantly different from both healthy musicians and non-musicians. Bayesian statistics, however, indicate weak evidence for the alternative hypothesis, i.e., differences between MD patients and healthy musicians as well as between patients and healthy non-musicians. Since the Bayes Factors in both comparisons are close to 1, these results rather indicate absence of evidence[34] than evidence for group differences. These inconclusive results might be explained by the small sample size of our study. Also, in order to make our results comparable to previous studies, we applied the widely used staircase method instead of randomized stimuli presentation which might have contributed to a potential

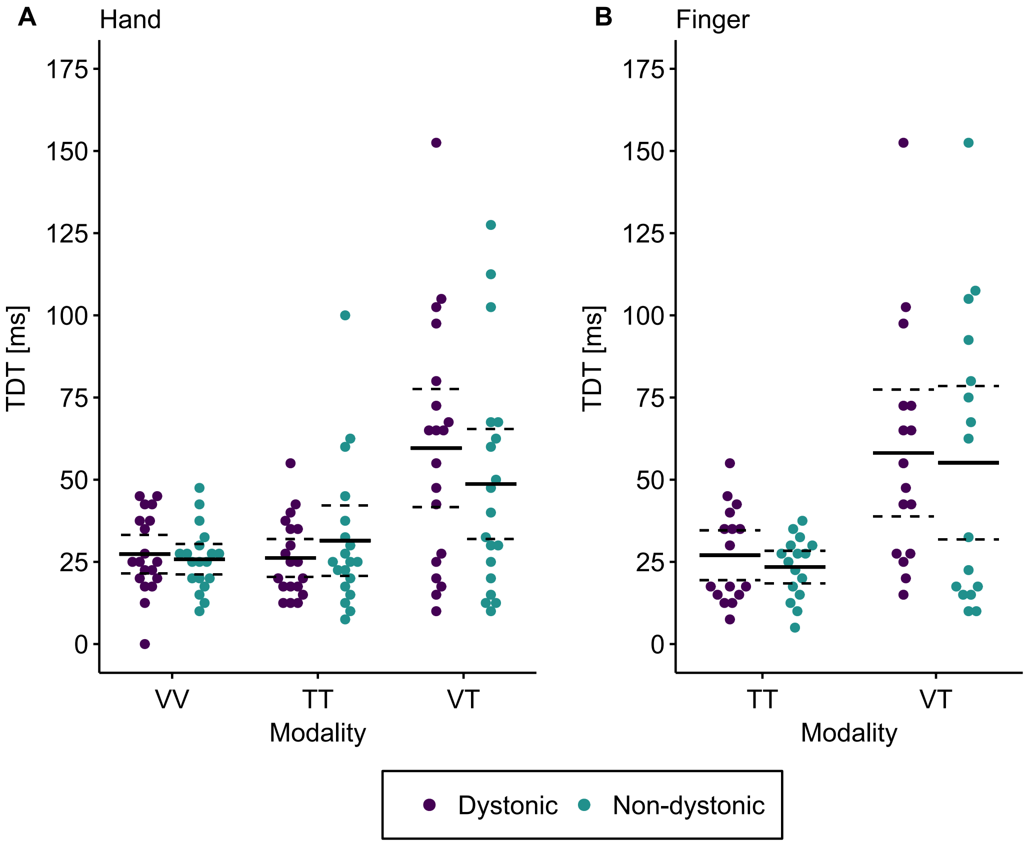

Figure 2. Temporal discrimination thresholds (TDTs) in dystonic and non-dystonic hands and fingers of patients with musician´s dystonia. (**A**) Comparison of visual (VV), tactile (TT) and visual-tactile (VT) TDTs in dystonic (purple) and non-dystonic (turquoise) hands in 19 patients with musician´s dystonia. (**B**) Comparison of tactile (TT) and visual-tactile (VT) TDTs in dystonic (purple) and non-dystonic (turquoise) fingers in 16 patients with musician's dystonia. Solid lines represent the respective mean. Dashed lines indicate the 95% confidence interval of the mean.

learning effect[12,39]. Additionally, we note a large variance of TDT values in our study, especially in the mixed visual-tactile task, thus making it difficult to detect differences between groups. A clear statement whether MD patients can reliably be distinguished from healthy musicians and non-musicians in terms of their TDT values therefore cannot be made.

Normal TDT levels in MD patients and healthy controls have also been shown in a former study[24], in which groups, however, were more heterogeneous compared to our study, as they pooled laryngeal and focal hand dystonia together in the MD sample and professional musicians as well as non-musicians in the healthy control group. In this study, neural correlates of visual TDTs and brain activity were investigated using resting-state functional MRI[24] in MD and non-musician focal dystonia patients as well as healthy (non-)musician controls. Whereas TDT values of MD patients did not differ from healthy controls, non-musician dystonia patients had significantly higher thresholds. In non-musician laryngeal and hand dystonia patients, an association, although not reaching significance, of TDT scores with lingual gyrus and cerebellar activation was found. In contrast, MD patients, show a distinctive pattern of correlations between TDT scores and brain activations (including the premotor, primary somatosensory, ventral extrastriate cortices, inferior occipital gyrus, precuneus and cerebellum). The authors concluded that by recruiting these different brain networks, MD patients seem to compensate for the lost neural correlates of TDT observed in healthy controls, which, in turn, could explain the normal TDT levels in patients[24]. A similar neural compensatory mechanism might have contributed to relatively normal TDT values in our MD patients, although we cannot prove this effect as we did not use neuroimaging methods. Also, in a TMS study comparing patterns of sensorimotor organization in the motor cortex in writer's and musician's dystonia, neurophysiological differences with increased functional connectivity between muscle representations and subsequent loss of spatial specificity were found in MD patients, but not in writer's dystonia[27]. Similarly, a study investigating neural correlates of different task-specific dystonia revealed decreased functional connectivity of the primary sensorimotor cortex, the parietal lobe and supplementary motor area in MD patients but not in non-musician's dystonia, including writer's cramp and spasmodic dysphonia[40]. These network changes suggest a weaker embedding of motor control and planning loops in MD but do presumably not affect TDT associated timing abilities.

Group	Variable	TDT scores		
		VV	TT	VT
Healthy musicians (n = 20)	Age of first instrumental practice	r_s = 0.23 (95% CI [− 0.25, 0.62]), p = 0.33	r_s = 0.088 (95% CI [− 0.38, 0.52]), p = 0.71	r_s = 0.48 (95% CI [0.04, 0.77]), p = 0.031
	Years of instrument playing	r_s = 0.15 (95% CI [− 0.33, 0.56]), p = 0.54	r_s = 0.17 (95% CI [− 0.31, 0.58]), p = 0.48	r_s = 0.22 (95% CI [− 0.26, 0.62]), p = 0.34
	Accumulated practice time	r_s = 0.035 (95% CI [− 0.43, 0.48]), p = 0.89	r_s = 0.17 (95% CI [− 0.31, 0.58]), p = 0.48	r_s = 0.16 (95% CI [− 0.32, 0.57]), p = 0.50
Musician's dystonia patients (n = 20)	Age of first instrumental practice	r_s = − 0.28 (95% CI [− 0.65, 0.20]), p = 0.23	r_s = − 0.027 (95% CI [− 0.47, 0.43]), p = 0.91	r_s = − 0.4 (95% CI [− 0.72, 0.06]), p = 0.078
	Years of instrument playing	r_s = − 0.22 (95% CI [− 0.61, 0.26]), p = 0.36	r_s = 0.13 (95% CI [− 0.34, 0.55]), p = 0.58	r_s = 0.12 (95% CI [− 0.35, 0.55]), p = 0.61
	Accumulated practice time	r_s = − 0.41 (95% CI [− 0.73, 0.05]), p = 0.073	r_s = − 0.11 (95% CI [− 0.53, 0.37]), p = 0.66	r_s = − 0.12 (95% CI [− 0.54, 0.35]), p = 0.62
	Disease duration	r_s = − 0.24 (95% CI [− 0.62, 0.24]), p = 0.32	r_s = 0.14 (95% CI [− 0.33, 0.56]), p = 0.55	r_s = 0.085 (95% CI [− 0.38, 0.52]), p = 0.72
	Age of dystonia onset	r_s = − 0.28 (95% CI [− 0.65, 0.20]), p = 0.24	r_s = − 0.26 (95% CI [− 0.64, 0.22]), p = 0.27	r_s = − 0.22 (95% CI [− 0.61, 0.26]), p = 0.35
	Time since last botulinum toxin treatment[a]	r_s = 0.043 (95% CI [− 0.65, 0.70]), p = 0.91	r_s = − 0.31 (95% CI [− 0.82, 0.46]), p = 0.41	r_s = 0.11 (95% CI [− 0.61, 0.73]), p = 0.77
	Neuroticism[b]	r_s = − 0.15 (95% CI [− 0.59, 0.36]), p = 0.56	r_s = − 0.16 (95% CI [− 0.60, 0.34]), p = 0.52	r_s = − 0.15 (95% CI [− 0.59, 0.35]), p = 0.56
	Extraversion[b]	r_s = 0.08 (95% CI [− 0.41, 0.54]), p = 0.75	r_s = 0.11 (95% CI [− 0.39, 0.56]), p = 0.66	r_s = − 0.19 (95% CI [− 0.61, 0.32]), p = 0.46
	Openness[b]	r_s = 0.16 (95% CI [− 0.34, 0.60]), p = 0.52	r_s = 0.041 (95% CI [− 0.45, 0.51]), p = 0.87	r_s = 0.066 (95% CI [− 0.43, 0.53]), p = 0.79
	Agreeableness[b]	r_s = 0.28 (95% CI [− 0.23, 0.67]), p = 0.27	r_s = 0.12 (95% CI [− 0.38, 0.57]), p = 0.63	r_s = 0.025 (95% CI [− 0.46, 0.50]), p = 0.92
	Conscientiousness[b]	r_s = − 0.19 (95% CI [− 0.62, 0.31]), p = 0.44	r_s = − 0.31 (95% CI [− 0.69, 0.20]), p = 0.21	r_s = − 0.13 (95% CI [− 0.57, 0.37]), p = 0.59

Table 2. Correlations between TDT scores and potentially influencing variables (musical activity variables, disease-related variables, NEO-FFI). r_s = Spearman rank correlation coefficients. 95% confidence intervals in parentheses. Different TDT modalities are indicated as visual (VV), tactile (TT) and visual-tactile (VT). [a]Data from 11 patients currently receiving treatment with botulinum toxin. [b]Data from 18 patients.

As former TDT studies revealed no difference between the visual and tactile protocol, and the visual-tactile protocol seemed to have a high variability[5,13], the visual protocol was solely used in further investigations, including studies with MD patients[23,24]. In contrast, we wanted to see whether the uni-modal visual task can be globally used as a biomarker of altered sensorimotor processing, or if tactile stimuli should be included to the analysis as patients with focal task-specific hand dystonia have proven alterations in spatial and temporal sensory discrimination[26,27]. Similar to the earlier results[5,13], we found significantly higher and more variable TDTs in the visual-tactile compared to the uni-modal tasks (visual and tactile) for all three groups, which might be due to an activation of additional brain regions in cross-modal processing tasks[41]. Contrary to our expectations, we found no interaction of modality and group, indicating that there is no difference in visual and tactile temporal processing in MD patients. Furthermore, although musical training generally improved timing abilities in healthy participants, we saw no influence on a specific modality. This finding strengthens the global applicability of uni-modal TDT tasks.

Additionally, we compared visual, tactile and visual-tactile TDT of the dystonic and non-dystonic hand as well as dystonic and non-dystonic fingers as neurophysiological studies showed abnormal homuncular organization of the finger representation with reduced inter-digit separation, reversal and overlapping activation in the primary somatosensory cortex of patients with focal hand dystonia[42,43]. Clearly, we found no difference between dystonic and non-dystonic fingers, which might be partially explained by the fact that it can be difficult to separate dystonic (typically flexion of fingers) and compensatory movements (usually extension of fingers) in clinical practice[44]. Also, the impression of a determinable dystonic pattern of specific fingers might not be transferable to the underlying pathophysiology and both dystonic as well as compensatory movements are part of a complex motor pattern. In addition, we neither found a difference between the dystonic and non-dystonic hand, nor interaction of hand and modality. A recent study[45] examined tactile space orientation evaluating distances between two touches across eight orientations on hands and forehead in different forms of isolated focal dystonia (cervical dystonia, blepharospasm and writer's cramp) mirroring structural organization of somatosensory receptive fields. Also, the authors found no difference in affected and unaffected body parts[45]. Comprehensive electrophysiological testing of somatosensory inhibition and cortical plasticity in patients with basal ganglia lesion-induced acquired dystonia revealed no difference compared to healthy controls, questioning the presence of widespread abnormalities of somatosensory organization as a substantial pathophysiological feature[46].

In our exploratory correlation analyses, we further investigated relationships between TDTs and its potentially influencing factors. In line with results of a previous study[24], disease related variables as age of onset and disease duration had no effect on TDT scores. Although it long has been supposed that injections of botulinum toxin A only have a local effect on neuromuscular transmission of treated muscles, recent studies in other types of focal dystonia, however, show temporary alterations on cortical and subcortical level[47]. Since eleven patients were still treated with botulinum toxin A at the time of study participation, we tested the correlation of time since last botulinum toxin injection and TDT scoring. Similar to previous studies[5,15], we did not find any relationship. In addition, another study compared TDT before and one month after botulinum toxin A injection in patients with cervical dystonia and did not find changes in TDT scoring[48]. It is therefore possible that the specific networks involved in TDT processing in MD are not affected by botulinum toxin therapy, although this remains speculative since, to our knowledge, there are no neurophysiological or neuroimaging studies investigating effects of chronic botulinum toxin treatment on the central nervous system in MD patients.

Furthermore, we analyzed to which extend musical activity influences different TDT modalities. Whereas duration of instrumental playing had no influence, the age of onset of instrumental practice correlated with the visual-tactile TDT in healthy musicians, indicating that a younger age of first practice is associated with a lower visual-tactile TDT. In early childhood neuronal plasticity is enhanced which is why early musical training enlarges sensory and association cortices, corpus callosum and auditory cortex improving visuomotor and auditory-motor synchrony[49,50]. In MD patients we see an opposite association, not reaching significance, towards a higher visual-tactile TDT in early trained patients which could be due to maladaptive plasticity with overlapping receptive fields[51]. Also, higher accumulated practice times seem to be associated with lower visual TDTs in patients, although this association did not meet significance. Longer hours of musical training might improve timing abilities and therefore also influence TDTs which is in line with a previous study showing that long-lasting musical training can improve timing abilities not only in auditory but also in visual domains[25]. However, it remains elusive why this association is not evident in tactile and visual-tactile stimuli or in the group of healthy musicians. The results of the correlation analyses should be interpreted with caution due to the low sample size of both musician´s dystonia patients and healthy musicians. To validate our exploratory correlation results and better estimate the strength of these effects, a bigger sample size would be needed.

It has been suggested that rather than sensory deficits of temporal processing, impaired decision-making might contribute to elevated TDT in cervical dystonia and that decision-making could be influenced by psychological comorbidities[52]. Previous studies reported psychological abnormalities in patients with MD. For instance, higher NEO-FFI neuroticism scores in female and higher openness scores in male MD patients compared to other isolated focal dystonias[53] and higher neuroticism scores compared to both healthy musicians and non-musicians[54] were found. As half of MD patients had signs of anxiety, perfectionism or stress in a former study, Ioannou and colleagues even postulated a new classification of 'high psychological effect' (HPE) MD and 'low psychological effect' (LPE) MD[55]. For the two subtypes, possible different pathophysiological paths were suggested: the LPE-MD might purely affect motor circuit, whereas the HPE-MD additionally involves emotional-memory and limbic networks of the cortical-basal ganglia-thalamic structures. In addition, the two subtypes should be considered in MD research as well as therapeutic management of patients[55]. To examine the relationship between personality profiles and TDT in our study, we correlated NEO-FFI and TDT scores and did not detect any correlations. However, data from patients with schizophrenia and major depression showed elevated acoustic TDTs compared to healthy controls, whereas dysthymic disorders seemed normal[56]. It therefore might be fruitful to investigate the relationship between TDT scores and psychological comorbidities (e.g., anxiety, depression) in MD patients in further studies.

In summary, we could replicate the results of earlier studies[23,24] finding lower TDT in musicians compared to healthy non-musician controls. In contrast, TDTs in our MD cohort cannot reliably be distinguished from healthy musician and non-musician controls, which might be due to small sample sizes and high variability of TDT values. Furthermore, TDT values in MD patients were neither influenced by dystonic status, musical activity, disease variables nor personality profiles. Our results suggest that TDT therefore seems not to be a reliable biomarker of impaired sensory processing in MD and might not be a useful endophenotype in clinical assessment of MD patients and their relatives.

Data availability

Anonymized data of the study are available from the corresponding author upon reasonable request of qualified investigators.

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Author contributions
F.B.: designed and conceptualized study, collected and interpreted the data, drafted the manuscript for intellectual content. M.H.: collected, analyzed and interpreted the data, drafted the manuscript for intellectual content. T.P.: acquisition of data, revised the manuscript for intellectual content. J.J.: acquisition of data, revised the manuscript for intellectual content. T.B.: designed and conceptualized the study, revised the manuscript for intellectual content. E.A.: acquisition of data, revised the manuscript for intellectual content. A.A.K.: interpreted the data, revised the manuscript for intellectual content. A.S.: designed and conceptualized study, interpreted the data, revised the manuscript for intellectual content.

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The authors declare no competing interests.

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Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Publikationsliste

Originalarbeiten

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Posterbeiträge

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