Function of the Ventral Premotor Cortex in Auditory-Motor Integration of Musical Rhythm

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Contents

1. Preface

”We listen to music with our muscles.”

Friedrich Nietzsche (Sacks, 2006).

The tendency of human beings to move in synchrony with an auditory rhythmical pulse is considered a cross-cultural universal (Nettl, 2000). Music and movement is intricately connected, and in some cultures, the term for music that refers merely to its acoustic component and excludes dance is even lacking. The link between auditory and motor systems seems exceptional when it comes to timing. While humans tend to tune in to an auditory beat by head nodding, toe tapping and humming, they do not feel the urge to spontaneously move to periodic visual pulses such as a bouncing ball (Zatorre et al., 2007). Remarkably, integration of auditory input and motor output is at the heart of what has been regarded as the most elementary function of the nervous system - the brain as a sensorimotor machine (Jeannerod, 1985; York & Steinberg, 1994). The simplest example of sensorimotor integration is that of a reflex that enables a living entity to move away from a source of sensory perturbation to preserve its own existence (Maturana & Varela, 1992). However, while this example of a discrete signal-response mapping has been uncovered in the simplest neuronal circuits, the coupling of movements to and predicting the timing of structured sequences of external events, mechanisms regarded as an integral part of music or speech, require a significantly more complex neurofunctional implementation. Although progress has been made with regard to the neural underpinnings of speech and music during the last century and in particular the last two decades in the advent of non-invasive neuroimaging techniques, it remains unknown, which neural mechanisms give rise to the urge and ability to accurately couple ones own movements to an auditory rhythm.

The present work experimentally addresses the contribution of a motor-related brain region with prominent connections to auditory areas, the ventral premotor cortex (PMv), to auditory-motor integration of musical rhythm. A combination of techniques - neuroimaging and non-invasive neuronal interference - is used to explore the causal role of the PMv in this auditory-motor timing mechanism.

The main aim of this thesis is threefold: Firstly, and most importantly, to probe the critical contribution of a motor-related region to both perceptual preference of and motor coupling to a musical rhythm; secondly, to identify additional neural mechanisms and networks that support auditory-motor timing; thirdly, to provide a model for auditory-motor integration of rhythm that incorporates the present experimental findings into a neuroanatomically sound framework of sensorimotor cognition and control.

The present thesis is structured into three major parts. The first provides a theoretical background of auditory-motor integration of rhythm initially from a behavioral perspective, which furthers the notion of an intricate connection between auditory rhythm and movement in humans. It continues with a neurobiological perspective on auditory-motor integration. The aim of the latter is to provide an overview of neuroanatomical and functional evidence leading to the assumption that a motor-related region in the dorsal auditory stream (Rauschecker & Scott, 2009; Hickok & Poeppel, 2007) - the ventral premotor cortex (PMv) - may contribute to the urge and ability to accurately couple ones own movements to auditory rhythms. The second part is the core of the present work. After a brief introduction of the methods employed in the empirical work, three experiments which test assumptions concerning the role of the PMv in auditory-motor integration are presented. *Experiment 1* (Kornysheva et al., 2010) uses functional magnetic resonance imaging (fMRI) to explore whether individual perceptual preference for musical rhythms is accompanied by activity in motor-related sites (i.a. the PMv) and to specifically identify those rhythmical properties that are associated with this activity increase. Moreover, it is tested whether such a boost in activity corresponds to that during an auditory rhythm task. This would imply that the activity increase in motor-related areas during preferred rhythm may be explained by enhanced sensorimotor simulation - a mechanism previously suggested for perceptual rhythm tasks. Using repetitive magnetic stimulation (rTMS), *Experiment 2* (Kornysheva et al., in press) further explores the above assumptions. However, in contrast to fMRI, transient interference with the PMv allows to probe the causal contribution of this area to rhythmic preference and perceptual rhythm tasks. Finally, *Experiment 3* (Kornysheva & Schubotz, submitted) uses rTMS to determine the causal role of the PMv to auditory-motor synchronization. Unlike the preceding experiments, it combines rTMS and fMRI to explore potential compensatory mechanisms of short-term functional reorganization after PMv disruption. Thus, besides neuroimaging which enables to identify brain activity that accompanies certain tasks and behaviors, interference with the ongoing activity in the PMv, as well as a combination of interference and neuroimaging is utilized in the present work. This allows to address the causal significance of the region of interest and to identify how the interference-related reorganization of brain function helps to preserve auditory-motor timing.

The final part summarizes and discusses the obtained findings in terms of the theoretical framework provided in the first part of the present work. The thesis outlines the limitations of the experimental findings and concludes with an outlook on possible future research directions related to auditory-motor integration of rhythm.

Part I.

Theoretical background: Auditory-motor integration of rhythm

2. Behavioral basis

”das Notwendigste und Härteste und die Hauptsache in der Musik (...) das Tempo”

Mozart, 1977 (Spohr, 1951).

2.1. Musical rhythm

There is no universally accepted definition of rhythm (Patel, 2008). It occurs in many contexts besides music, such as speech, brain oscillations, circadian rhythms. Involving temporal regularity of events, rhythm can be regarded as a subtype of temporal processing. The latter can occur on different time scales: microseconds (e.g. sound localization), milliseconds (motor coordination, speech, music), seconds to minutes (decision making, conscious time estimation) and hours (circadian rhythms) (Mauk & Buonomano, 2004). These time scales have been shown to be sub-served by differential neural mechanisms (Buhusi & Meck, 2005; Lewis & Miall, 2003), however, their neural implementation is still debated.

Musical rhythm can be distinguished from the above by two main temporal features: Firstly, in contrast to the above-mentioned biological rhythms, elements of a musical rhythm consist of events with an inter-onset-interval in the sub-seconds to seconds range (millisecond timing), similar to speech. However, unlike the latter, music typically consists of repetitive temporal patterns (Nettl, 2000).[1]

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[1] Pike (1945) proposed that speech rhythm of different languages fell into one of two rhythmic

A subtype of auditory repetitive temporal patterns is an isochronous (evenly spaced) musical pulse (also ”beat”). It is prevalent across many musical styles and cultures (Wallin et al., 2001). Isochronous time marking in an incoming auditory stimulus allows to predict where the next beat is going to fall. In a variety of musical styles the isochronous pulse typically occurs around two cycles per second (120 beats per minute (BPM); Moelants (2003)), which coincides with the rate of repetitive movement such as walking (van Noorden & Moelants, 1999), or spontaneous tapping (Fraisse, 1982). Both its predictability and time range makes the musical pulse a cardinal cue for coordinating the movement of several individuals in a synchronized performance. The tendency and the ability of human beings to move in synchrony with a rhythmical pulse is considered to be a cross-cultural universal (Nettl, 2000; Patel et al., 2009).

The present work focuses on the neural basis of auditory-motor integration of this common subtype of musical rhythm - the beat. It is important to specify how the terminology is used in the present work: While the more general term *pulse* can be applied to an isochronous rhythmic event in different modalities (auditory, visual, tactile), the term *beat* is confined to the auditory domain. Furthermore, the term *beat rate* will be used interchangeably with *tempo*. The former can be used beyond the musical domain, i.a. referring to the rate of an isochronous auditory pulse (e.g. a metronome click) and the latter is bound to the auditory pulse of a musical rhythm.

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classes. While in ”stress-timed” languages such as English and German, stressed syllables were claimed to occur at regular temporal intervals, in ”syllable-timed” languages such as Italian and French, syllable onsets were claimed to be evenly timed. This proposal entails that speech consists of equally-spaced (isochronous) patterns, the only difference being the units that occurred periodically. However, experimental support for isochrony in speech is lacking (Patel, 2003; Grabe & Low, 2002). Note that there are exceptions in music, as well: 20th century Western musical tradition, e.g. serial compositions in which intervals between tones, as well as pitch is governed by a predetermined series of digits; 2,000-year old Chinese musical tradition Ch’in, notations of which contains no time markings for individual notes (Patel, 2008).

2.2. Auditory rhythm and movement induction

2.2.1. Auditory-motor integration in humans

Auditory-motor coupling can be said to involve the temporal coordination of a motor rhythm with an external rhythm (Repp, 2005). How do humans entrain to a periodic beat? In most studies, to assess auditory-motor synchronization abilities, finger tapping, typically the index finger is used as a measure of motor response. This is partly due to the fact that finger tapping measurements can be conducted with a basic experimental setup, so that there is no need for additional equipment - in the simplest case via a standard response button. However, humans typically perform whole body movements, foot tapping or head nodding when they spontaneously tune in to a rhythm. In contrast to finger tapping, such movements can be observed in infants when they spontaneously entrain to a musical beat (Zentner & Eerola, 2010). In particular, the vestibular system, that is stimulated by head and whole body movement, has been suggested to be important with respect to auditory-motor integration of rhythm. In both infants and adults, active or passive movement (bouncing) compared to movement observation has been shown to bias the perception of an ambiguous rhythm (Phillips-Silver & Trainor, 2005, 2007). Moreover, in adults passive motion of the head alone affected auditory encoding, whereas passive motion of legs did not (Phillips-Silver & Trainor, 2008). Although finger tapping does not entail vestibular information, it can, nevertheless, be regarded as reflecting the auditory-motor component of synchronization.

A central feature of auditory-motor synchronization is the negative asynchrony: finger taps tend to precede sequence tones by a few tens of milliseconds, rather than being distributed symmetrically around the tone onsets (Repp, 2005). This effect seems to be more pronounced when subjects synchronize to isochonous auditory clicks compared to beats embedded in a musical context, i.e. when the pulse is surrounded by other rhythmic events. The causes of negative asynchrony are poorly understood. Negative asynchrony decreases when external auditory feedback from taps is provided (Aschersleben & Prinz, 1995), and it increases when the latter is delayed (Aschersleben & Prinz, 1997) or when the tactile feedback from the finger is reduced through anesthesia (Aschersleben et al., 2001). One cause may be a slower central registration of tactile and proprioceptive information, as compared to auditory information suggesting that the negative asynchrony may be caused by different nerve transmission delays from the finger to the brain and from the ear to the brain. This is in line with the Paillard-Fraisse hypothesis (Fraisse, 1980) which main assumption is that the perception of clicks and the generation of taps rely on a shared central timeline. Accordingly, if the tap is to coincide with the metronome click on a central timeline, then the tap has to precede the click to mitigate the effect of nerve transmission delays. This assumption was further supported by findings that the negative asynchrony is larger for foot tapping than for manual tapping (Aschersleben & Prinz, 1995). However, the decrease of the negative asynchrony with increasing tempo and the presence of additional rhythmic patterns cannot be explained by the above assumptions (Repp, 2005).

Importantly, preceding or perfectly synchronous tapping suggests that subjects possess an accurate prediction of an upcoming beat. A possible underlying prediction mechanism is proposed below (cf. Fig. 2.2 and 2.3).

Finally, rhythmic sequences may or may not be beat-based, i.e. they may or may not consist of multiples of an inter-onset-interval between two beats. Moreover, in beat-based rhythms, the beat is not always externally paced, but has to be interpolated internally. Since beat-based rhythms enable temporal intervals to be encoded as multiples or subdivisions of the beat, rather than as unrelated intervals, this mechanism may be analogous to chunking. The latter is a way of grouping components into a single unit (or chunk) to increase the ability to extract information from the environment, in spite of limitations on working memory (Gobet et al., 2001; Miller, 1956). Accordingly, the comparison of beat-based versus non-beat-based rhythms revealed a superior ability of rhythm discrimination and synchronization (Patel et al., 2005; Hebert & Cuddy, 2002; Grahn & Brett, 2007; Grahn, 2009). Although the present work will explore auditory-motor integration of rhythms with an *externally paced* beat, the above evidence underlines the beneficial effect of beats on auditory-motor integration, as well as a superior encoding of a beat in a rhythmic sequence.

2.2.2. Developmental perspective on auditory-motor integration

Is auditory-motor coupling to a regular beat innate or learned? Although it has been proposed to be a cross-cultural universal (Nettl, 2000), the fact that most studies were preformed with an adult population does not allow to conclude that this is an innate behavior. On the contrary, several studies with infants suggest that beat perception and auditory-motor coupling to a beat is a culturally acquired, or at least a culturally influenced behavior. Humans entrain to the beats differently depending on their cultural origin. Their enculturation to rhythm begins during infancy: While at 6 months North American infants respond equally to disruptions of Western and Balkan rhythm ratios, the latter are consistent with both isochronous (i.e. 2:1 and 1:1) and non-isochronous (i.e. 3:2) rhythms, they fail only with Balkan rhythms by 12 months (Hannon & Trehub, 2005a,b). Also, auditory preference for a beat rate is influenced by prior movement. Phillips-Silver & Trainor (2005) revealed that bouncing infants in a specific tempo to a rhythm with an ambiguous beat rate, determines there subsequent perceptual preference of a beat rate.[2], since infants listened longer to rhythmic patterns that matched the patterns to which they were bounced beforehand. Also, it is important to emphasize that accurate synchronization behavior, i.e. the alignment of movement with the auditory cues, emerges only around preschool age (Drake et al., 2000; McAuley et al., 2006; Zentner & Eerola, 2010; Eerola & Luck, 2006).

Nevertheless, a rudimentary form of beat perception has been reported in neonates in an event-related potential (ERP) study (Winkler et al., 2009). Omitting the downbeat elicited brain activity associated with violating sensory expectations. Moreover, like adults, infants as young as 7 months infer an underlying beat, categorizing rhythms on the basis of beat subdivision (reported as meter) (Hannon & Johnson, 2005). A recent study demonstrated 5-24 months old infants spontaneous entrainment to beat-based auditory rhythms versus infant or adult directed speech (Zentner & Eerola, 2010), although synchronization was rudimentary. Interestingly, the preference for beat rates for entrainment has been shown to be influenced by age-related slowing of event timing (McAuley et al., 2006). The data suggests that children appear to operate on a faster time scale than adults, since they prefer to listen to fast sequences and to tap at fast beat rates which changes gradually with age. This finding corresponds to the proposed impact of anthropometric factors which covary with speed of locomotion on beat rate preference (Todd et al., 2007).

Taken together, the above evidence suggests that there is a rudimentary innate phylogenetic and ontogenetic basis for auditory-motor integration of rhythm. However, throughout development, it becomes increasingly specialized for encoding the musical structure of a particular culture (Hannon & Trainor, 2007).

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[2] Note that the influence of beat rate and beat subdivision cannot be separated in this study, since beats rate was faster in a 4/8 (2 beats) compare to 3/8 (1 beat) metre (grouping of beats, or beat subdivisions).

2.2.3. Auditory-motor integration of rhythm in non-human primates

Until today there has been no evidence for primates being able to synchronize to an auditory cue. A study with three macaques trained over several months by Zarco et al. (2009) demonstrated that the monkeys could attend to a synchronization-continuation task and produce tapping intervals that were modulated by interval changes of visual or auditory cues. However, humans showed superior timing abilities in both components of the task. Most importantly, even following extensive training, in contrast to humans, monkeys showed no negative asynchrony during the synchronization phase, but a response lagging around 300 ms behind the auditory or visual cues, respectively, suggesting a reactive rather than a predictive mechanism of sensorimotor integration. Despite the fact that these asynchronies were smaller than in a serial reaction time task (Zarco et al., 2009), these findings strongly suggest the lack of top-down modulations. Finally, only humans showed smaller inter-onset-variabilities with regard to auditory-motor compared to visuo-motor synchronizations. The latter suggests that the superior capacity for accurate auditory-motor coupling in humans is unique among primate species.

The lack of auditory-motor synchronization abilities in non-human primates is in line with the absence of speech communication in these species. Like auditory-motor timing, speech comprehension and production requires a temporally precise transformation and matching of auditory, somatosensory and motor informations across a sequence of events. This strongly suggests differences in neural networks enabling auditory-motor transformation, elucidated in Chapter 2.

Note that in contrast to non-human primates, some bird species have been shown to possess auditory-motor synchronization capabilities (Patel et al., 2009; Schachner et al., 2009). The respective behavioral hypothesis put forward states that only animal species with vocal learning and mimicry in their behavioral repertoire are capable of auditory-motor coupling.

2.3. Internal forward model of auditory-motor integration of rhythm

Humans often move when they listen to an auditory rhythm, suggesting motor networks may be important during rhythm perception. At the same time, behavioral findings demonstrating negative asynchrony in auditory-motor entrainment, as well as accurate performance in rhythm discrimination tasks suggest predictive mechanisms in both rhythm perception and synchronization. Taken together, this behavior lends support to a framework of ”internal models” (also ”simulation” or ”emulation”) as proposed in motor control theory with regard to forward models (Grush, 2004; Wolpert & Flanagan, 2001), that incorporate the notion of predictions generated by the motor system with regard to the outcome of the performed movement (Fig. 2.1).

The motor system sends a motor command to the periphery/body, together with a copy (efference copy/corollary discharge) of this motor command, which leads to a generation of predictions regarding the most probable outcome of the prospective action on the basis of the current state of the system. The accuracy of the forward model is evaluated through the comparison of the actual and predicted sensory feedback. A small prediction error is equivalent to an attenuated output of the comparator, which signals the sensory discrepancy. This can be conceived as a sensory gating or cancellation mechanism, with attenuated sensory responses in the case of accurate prediction.

This model is dynamic in such a way that it allows to update the forward model in

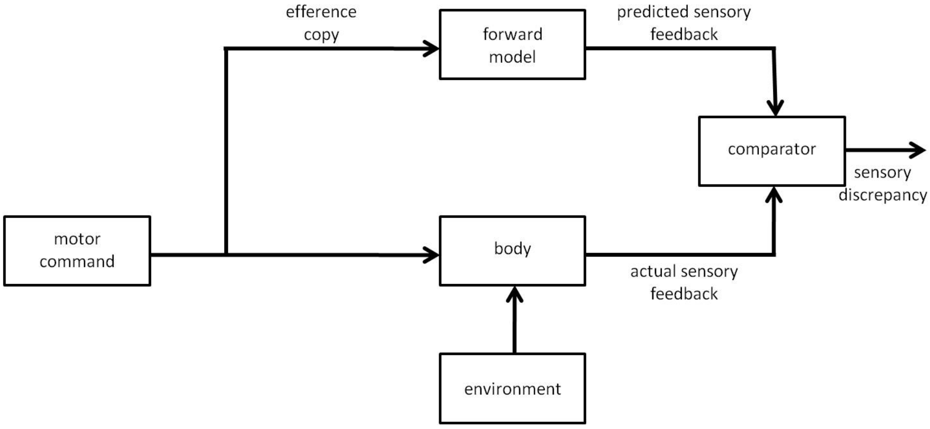

Figure 2.1.: *Forward model in motor control. Adapted from Wolpert & Flanagan (2001).*

case of a mismatch between predicted and actual feedback. The sensory prediction error from a given forward model is conceived to be represented as a probability. Accordingly, if the error is small then the probability that the forward model is appropriate is high (Wolpert & Flanagan, 2001).

If we were to rely on sensory signals alone, accurate and fast motor control would be impossible. The reason is that sensory signals are prone to noise and delayed due to receptor transduction, as well as neural conduction from the periphery. In fast movements and movement sequences, this could lead to erroneous estimations of the state of the system, thus potentially leading to instability. The advantage of internal forward models is that the estimate is made ahead of the movement and the actual sensory input. At the same time, a drift of the estimate is prevented by the actual sensory feedback via the sensory discrepancy. In addition to coordination of movements and movement sequences, in motor control, these models explain how the agent system can differentiate between externally (environmentally-) and internally (self-) induced sensory input. If the latter results from self-produced movement, the actual sensory discrepancy is attenuated compared to external input, as in tickling (Blakemore et al., 2000).[3]

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[3] This idea of a corollary discharge is not new. It originates from Helmholtz study of eye movement,

This computational perspective on motor control, specifically sensorimotor simulation via internal forward models, has been applied to cognitive functions beyond the action domain (Grush, 2004; Schubotz, 2007). It is based on the assumption that the motor system may play a core role in the prediction of externally induced events, as well as in other, i.a. social cognitive functions (Wolpert & Flanagan, 2001).

How can internal forward models explain auditory-motor integration behavior? Figures 2.2 and 2.3 propose a mechanism of rhythm prediction and auditory-motor

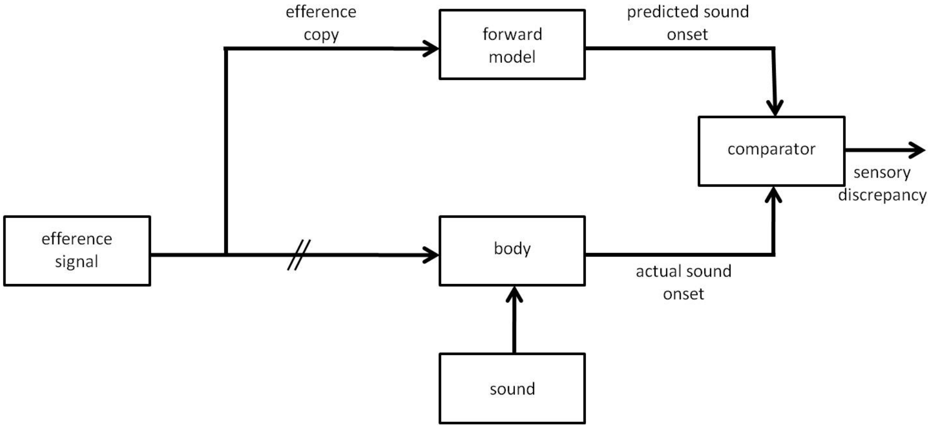

Figure 2.2.: *Internal forward model of auditory rhythm prediction*

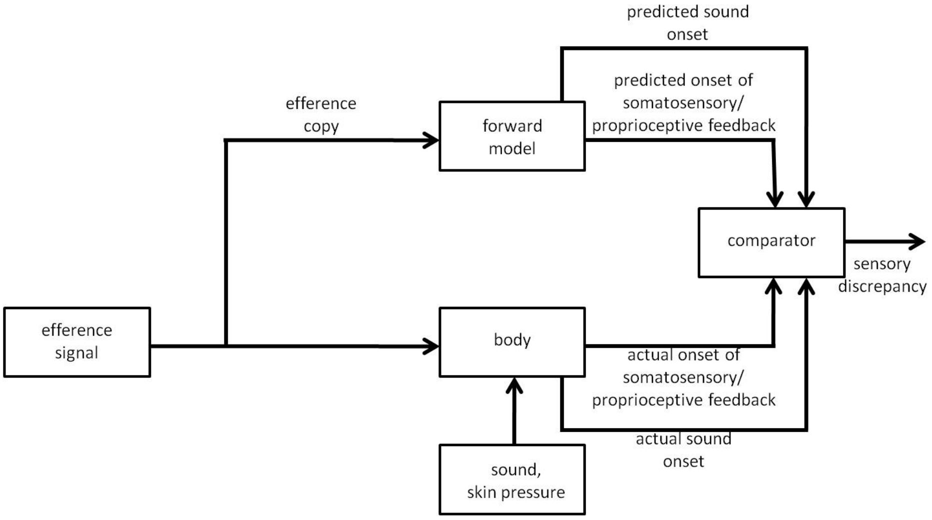

Figure 2.3.: *Internal forward model of auditory-motor synchronization*

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who hypothesized that the illusion of a stable world on the retina arises from the predicted gaze position which is based on a copy of the motor command acting on the eye muscles (Wolpert & Flanagan, 2001).

synchronization on the basis of internal forward models.

In rhythm prediction, the efferent signal from the motor system is not transmitted to the body. Since no movement takes place, there is no additional actual proprioceptive or somatosensory feedback (reafference; sensory signal resulting from own actions) or prediction of this feedback. However, an efference copy of this efferent signal is send to trigger those forward models that are restricted to the temporal aspects of the auditory domain.[4] Accordingly, the sensory discrepancy that results from a difference between the predicted and the actual onset of a sound (exafference; sensory signal from the environment) updates the forward models that predict the expected timing of the upcoming auditory input.

Auditory-motor synchronization adds at least two additional information channels on top of the above-mentioned auditory channel. Let us take an example of finger tapping to a beat. The efference signal is send to the periphery. The finger is in turn transmitting reafferent signals on the actual onset of somatosensory input and of the target position of the finger relative to the rest of the body (proprioceptive input) in addition to the actual exafferent signals on the onset of the beat. An efference copy of the efferent signal to the periphery triggers forward models predicting either the timing of the auditory or the timing of somatosensory and proprioceptive input. Finally, the sensory discrepancy with regard to the predicted and actual timing of these events is computed for each modality. In addition, accurate synchronization requires the comparison of exafferent auditory with reafferent proprioceptive and somatosensory onset, presumably on a shared central timeline according to the Paillard-Fraisse hypothesis (Aschersleben & Prinz, 1995, 1997; Fraisse, 1980), Ascherleben and Prinz 1995, 1997).

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[4] The hypothesized isolation of temporal forward models is in line with the fragmentation of function demonstrated for a variety of brain regions, e.g. for the visual (Zeki, 1978) or premotor cortices (Rizzolatti et al., 1988). More specifically, evidence for a fragmentation of rhythmic functions have been provided by patient studies demonstrating amusia for rhythm, but not for pitch or for other properties of auditory musical sequences (Peretz, 2001).

Returning to the beginning of this section, the application of internal forward models to auditory-motor timing concurs with a common observation in tapping experiments, namely that the taps precede auditory beats in rhythmic sequences during auditory motor synchronization (negative asynchrony). Moreover, this account seems to be in line with the tendency of human beings to move in synchrony to a rhythmical pulse: Forward models exploit the motor system for prediction of rhythmic events that are in the time range of repetitive movements like walking, as mentioned earlier. Thus, the frequent spontaneous tuning-in to the beat of periodic rhythmic sequences by whole body movement, head nodding and foot tapping may be directly associated with an enhanced involvement of the motor system. Accordingly, listening to rhythmic beats may lower the motor threshold due to the use of the motor system for the prediction of auditory timing, which may ultimately lead to an overt motor synchronization to the beat.

3. Neurobiological basis: The ventral premotor cortex (PMv)

A motor-related region - the ventral premotor cortex (PMv) - is the main focus of the current experimental work on the neural basis of auditory-motor integration of auditory rhythm. Why? The following theoretical account on anatomical and functional properties of the PMv will provide the foundation for the hypothesized significance of this region in auditory-motor integration of rhythmic sound sequences during both listening and synchronization.

3.1. Anatomy

> "(...) seeking to understand function, it is usually a good idea to study structure." (Crick & Koch, 2005).

Each brain area has a unique pattern of inputs (afferent projections) and outputs (efferent projections) - a so-called connectional fingerprint (Passingham, 2007; Passingham et al., 2002). Whereas the afferent and efferent connections of the PMv reveals the information it receives and the areas it influences, respectively, its intrinsic structure and connectivity discloses how this region operates on the information it receives, in other words, what it does to transform input into output.

Both the current knowledge on the structural properties of the PMv, as well as on its anatomical projections to other brain regions that have been repeatedly shown to be involved in the processing of auditory rhythm, are introduced in the following sections.

Despite the lack of evidence for vocal learning and auditory-motor coupling in the behavioral repertoire of non-human primates, both human and non-human primate anatomy is considered in the following sections. The non-human primate brain does not always exhibit clear-cut anatomical homologies with the human brain due to changes that occurred in brain evolution. However, non-human primate studies provide what is mostly missing in humans - a meticulous knowledge about the structure of a region by cellular labeling, and about the origins and terminations of multisynaptic projections by multiple tracer techniques. Thus, organization and subdivision of cortical and subcortical regions that has been largely preserved across species helps to fill the blanks in human neuroanatomy. In the case of anatomical features specific to humans, differences to non-human primates are discussed and anatomical evidence is confined to studies on the human brain. Accordingly, the integration of these information resources from human and non-human primate anatomy furthers the knowledge of the structure and connectional fingerprint of brain areas such as the PMv in humans.

3.1.1. Structure

The cerebral cortex contains six cytoarchitectonic layers. The relative size of the layers differs according to their connectivity with other cortical, as well as subcortical regions, and ultimately according to the function of the respective cortical region: Layer I consists mostly of axons that run parallel to the cortical surface. Layers II and III contain pyramidal cells that projects to other cortical areas. Layer

IV contains interneurons and terminations of most of the inputs from the thalamus to the cortex. Its pyramidal cells send their axons back to the same thalamic nucleus that supplied the inputs, thus forming cortico-thalamic loops. For instance the sensory cortex has a thick layer IV because of its large number of thalamic inputs. Layer V houses large pyramidal cells, which project to the spinal chord, brain stem, and subcortical nuclei. This layer is prominent in the primary motor cortex, because it transfers signals to the periphery to initiate movement.

Cytoarchitectonically, the frontal lobe of primates can be very roughly described as consisting of two major regions: a rostral and a caudal. The rostral, prefrontal region is characterized by a six-layered structure. In some of its subregions the granular layer IV is well developed, in others, it is only rudimental. The caudal, premotor and primary motor part is characterized by the absence of layer IV, and is therefore classified as an agranular cortex (Rizzolatti, 2000). While the primary motor cortex is characterized by the presence of large pyramidal cells in layer V that project directly to the spinal chord, in the premotor cortex these are largely missing. Within the premotor cortex there is a further cytoarchitectonic differentiation: while the dorsal area 6 has larger pyramidal cells and a higher myelin content than ventral 6, the ventral 6 is also characterized by an incipient granular layer IV, which is virtually absent in dorsal area 6 (Barbas & Pandya, 1987). These architectonic features indicate that dorsal 6 is more akin to the motor cortex, whereas ventral area 6 is more closely related to sensory cortex (Barbas & Pandya, 1987).

This subdivision of the premotor cortex into a dorsal and a ventral part support the theory on the evolution of the structure of the cerebral cortex proposed by Sanides (1962) based on the cyto- and myelo-architectonic data. It hypothesized that new fields arise from phylogenetically older regions resembling them structurally. Accordingly, three so-called ”protogradations” affected the frontal cortex of primates: a medial originating in the cingulate gyrus and extending into the PMd, a lateral,

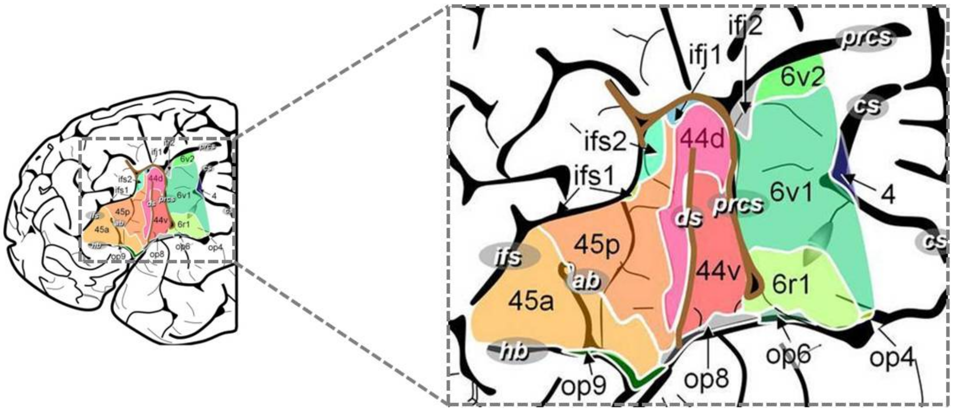

Figure 3.1.: *Subdivision of the PMv and adjacent areas according to Amunts et al. (2010).*

originating in the insular cortex and extending into PMv and inferior frontal cortex, as well as a more recent one, originating in the central sulcus. The first two protogradations differentiate in their anatomical relationships with the major subcortical structures, the basal ganglia (medial protogradation) and the cerebellum (lateral protogradation), respectively. With respect to layer IV, the third protogradation followed the principle of gradation from agranular (motor) to dysgranular to granular (prefrontal) cortex.

In the present work, the PMv is defined according to Preuss et al. (1996) and to a recent anatomical parcellation study by Amunts et al. (2010) as the premotor region below the (virtual) continuation line of the inferior frontal sulcus, bordered by the BA 44 rostrally and the BA 4 caudally.[1] More specifically, the PMv can be differentiated into two to three subdivisions on the basis of the distribution patterns of six receptor types that were quantified using in vitro receptor autoradiography (Fig. 3.1). According to Amunts et al. (2010), the PMv consists of a superior area 6v2, an inferior area 6v1, both being agranular, and showing the typical cytoarchitectonic laminar pattern of area 6 as described by Brodmann (1909). In addition, the authors identified a transitional area 6r1 in the precentral sulcus rostral, inferior to the ad-

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[1] This is in contrast to Rizzolatti et al. (2002) suggesting the devision of PMv and PMd at the upper limit of the frontal eye fields in humans.

jacent 6v1 and bordering the ventral part of BA 44 (Broca's area). It is transitional in the sense that it shares cyto- and receptorarchitectonical features with both area 44 and area 6, i.e. it contains both granular cells as well as a relatively prominent layer V. This finding is taken as further evidence for the hypothesis that the abilities associated with Brocas region might have evolved from premotor functions (Fazio et al., 2009).

The above additional subdivision of the PMv is also substantiated by a parcellation study based on diffusion tensor imaging DTI and fMRI, revealing two distinct portions of the PMv, according to its connectivity pattern and functional specialization (Schubotz et al., 2010).

3.1.2. Intrinsic connectivity: premotor and primary motor cortices

In macaques, above 60% of connections in the PMv (area F4 and F5) are intrinsic (Matelli & Luppino, 2001), which may point to their importance in the coordination of simultaneous preparation of movements involving several effectors, like hand and mouth movements. However, while in the lateral premotor cortex interconnections within the PMv and PMd are abundant, there is only scarce evidence on projections of the ventral to the dorsal premotor cortex (PMd), which is in line with the distinct evolutionary origins of these regions proposed by Sanides (1962), as referred to above.

Efferents Besides the projections within the PMv, this area sends its output to the primary motor cortex (Dum & Strick, 1991, 2002). Note that direct corticospinal projections have also been reported form this area, just as from other premotor sites (Dum & Strick, 1991). Accordingly, all premotor areas can influence movement both via efferent projections to the primary motor cortex and, directly, via projections to the spinal chord. In squirrel monkeys, anterograde tracers injected into the distal forlimb representation of the PMv revealed only sparse output to the SMA and the PMd (Dancause et al., 2006).

Afferents Injection of retrograde tracers in the superior PMv in monkeys revealed labeled cells in several motor-related areas: area 4 (primary motor cortex) that were localized at its caudal part, close to the central sulcus, supplementary motor area (SMA)[2], the precentral operculum, as well as extensive intrinsic connections in ventral PMv sites (Kurata, 1991). Only sparse input is reported from the PMd, however some connections are reported from hindlimb to forelimb representations, and forelimb to face representations (Ghosh & Gattera, 1995).

3.1.3. Extrinsic connectivity

3.1.3.1. Primary auditory and auditory association cortices

The connection between the posterior auditory cortex and the frontal cortex - the ”arcuate fasciculus” (AF) - has been described in prominent accounts with respect to speech function (Geschwind, 1970). Typically, a disruption of this pathway entails the so-called ”conduction aphasia”, a selective impairment of speech repetition with preserved comprehension and fluent production, which, however is paraphasic, i.e. shows speech with phonemic or word substitution (Anderson et al., 1999). According to current literature, the AF pathway is more complex than previously assumed. Three partitions have been reported in humans (Catani & Mesulam, 2008): In addition to the long direct segment connecting posterior STG with premotor and prefrontal areas, there is an indirect pathway consisting of two segments, an ante-

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[2] Notably, the respective study found that the PMd receives considerably more afferents from the SMA than the PMv.

rior segment linking frontal territories with the inferior parietal lobule (according to Schmahmann & Pandya (2006), the superior longitudinal fasciculus III (SLF III) in monkeys) and a posterior segment linking the inferior parietal lobule with posterior STG (Catani et al., 2005).

Auditory information is transferred to premotor areas via the the AF, which connect the superior temporal and the inferior parietal lobes with the lateral precentral gyrus - the so-called “dorsal auditory stream” (Hickok & Poeppel, 2004, 2007; Rauschecker & Tian, 2000; Rauschecker & Scott, 2009). Numerous recent diffusion tensor imaging (DTI) studies confirmed the dorsal pathway connecting these regions in the human brain (Catani et al., 2007, 2005; Glasser & Rilling, 2008; Saur et al., 2008; Rilling et al., 2008; Bernal & Ardila, 2009), which appears to be more prominent in the left hemisphere in the majority of the population (Catani et al., 2007).

While DTI allows to visualize fiber tracts in the brain by measuring the local anisotropy of water molecules in biological tissue occurring more rapidly in the direction aligned with the internal structure, it cannot demonstrate origins and terminations of fiber pathways. Usually, tracer studies in non-human primates provide information on the directionality and the relay stations of a pathway. However, unlike several other fiber tracts, there is no evidence on direct connection between auditory and ventral premotor sites in monkeys (Schmahmann & Pandya, 2006), in contrast to the ventral prearcuate (i.e. prefrontal) zone (Chavis & Pandya, 1976; Deacon, 1992). Specifically, the AF is known to project to dorsal area 8, dorsal prefrontal area 46, and the dorsal part of area 6, but not to the PMv. Only an indirect pathway (SLFIII) originating in the rostral portion of the inferior parietal lobe and the adjacent parietal operculum projects to the PMv and the adjacent area 44.

Accordingly, differences in the trajectory of the arcuate between humans and macaques have been revealed. In a comparative DTI study, Rilling et al. (2008)

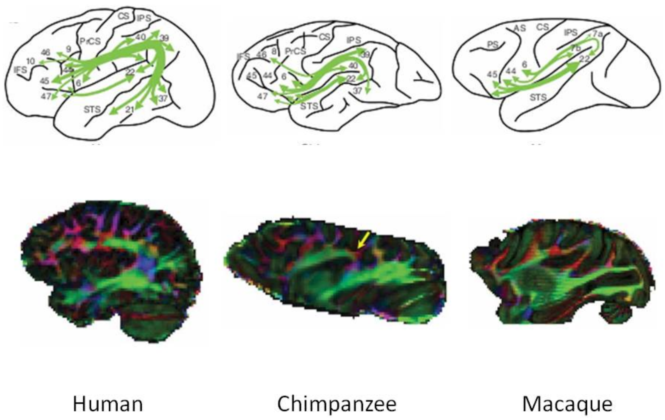

Figure 3.2.: *Connection between auditory and frontal areas in humans, chimpanzees and macaques. Yellow arrow points to red, mediolaterally oriented fibres in chimpanzee brain. Adopted from Rilling et al. (2008)*

suggest that humans show prominent interconnection between superior temporal and premotor, as well as prefrontal regions, whereas chimpanzees and macaques do to a much lesser extent. The lack of evidence for connections between the auditory and premotor areas is most probably associated with the lack of vocal and speech learning in monkeys Bernal & Ardila (2009), and so far no evidence has been demonstrated on auditory-motor synchronization by body movement in non-human primates. Alternatively, it is feasible that the inferior PMv in humans, in particular its rostral part extending (BA 6/44) is homologous to what is considered to be the ventral prefrontal cortex in monkeys. As mentioned before, Deacon (1992) reports a ventral prefrontal region to be dominated by auditory projections. Moreover, Kohler et al. (2002) found 13% of investigated neurons in area F5 to be audiovisual-motor (mirror) neurons.

Despite the lack of information on the anatomical connections through tracer studies, neurophysiological findings in humans indicate the presence of afferent, as well as efferent projections from PMv to the posterior STG. A recent study recording electrocorticograms time-locked to cortical electrical stimulation, revealed that information is transmitted bidirectionally, i.e. also from precentral back to temporal and parietal regions (Matsumoto et al., 2004). These results challenge the traditional notion of a mono-directional posterior to anterior flow of information in the arcuate fasciculus (Geschwind, 1970). This evidence for a bidirectional information flow indicates that motor information is important for perception, as suggested with respect to language (Liberman et al., 1967; Liberman & Whalen, 2000).

3.1.3.2. Cerebellum

The cerebellum and the basal ganglia are two major subcortical structures that influence movement, as well as cognition and affect (Bostan et al., 2010; Ramnani, 2006; Strick et al., 2009). Both structures form multisynaptic loops with the cerebral cortex.

In general, the cerebral cortex is heavily interconnected with the cerebellum, which, as suggested in the last decade, occurs not via open[3], but via closed[4] loops (Kelly & Strick, 2003; Ramnani, 2006; Strick et al., 2009). Accordingly, the cortex projects to the cerebellum via the pontine nuclei in the brainstem and crossing to the other hemisphere to granule and subsequently to Purkinje cells. On the other hand, the cerebellum projects back to the cortex via deep cerebellar nuclei and the thalamus (cf. Fig. 3.3 for a schematic display of the cortico-cerebellar circuit).

Efferents Regions with the most cortico-pontine projections are the frontal motor-related cortices (Glickstein et al., 1985; von Monakow et al., 1981). The premotor cortex (area 6 including its ventral part) is roughly equivalent to the primary motor cortex (area 4) in the density of its projection to the pons. Accordingly, in the frontal cortex, the high concentration of labeled cells in area 4 continues anteriorly in area 6 and decreases at the 6/8 border and is even sparser rostral to area

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[3] The notion that of all cortical sites that project via the pons to the cerebellar cortex only the motor cortex is in turn targeted by cerebellar output.

[4] The notion that all cortical sites that project via the pons to the cerebellar cortex are in turn targeted by cerebellar output.

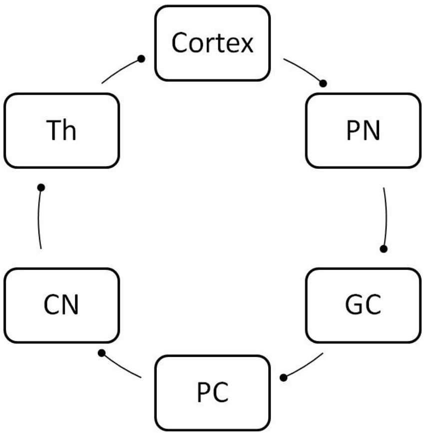

Figure 3.3.: *Schematic diagram of the multisynaptic cerebro-cerebellar circuit. Adapted from (Kelly & Strick, 2003). CN, Cerebellar nuclei; PC, Purkinje cells; GC, granule cells; PN, pontine nuclei (brainstem); Th, thalamus*

8, in area 9 of the frontal granular cortex (Glickstein et al., 1985). Mostly, these cells project to the lateral lobules IV-VI, in line with the notion of a closed-loop architecture (Kelly & Strick, 2003).

Afferents Primate studies utilizing transneuronal virus tracers demonstrated distinct multisynaptic projections of the cerebellum to the arm area of the PMv (Middleton & Strick, 1997). The projections could be traced back as far as to Purkinje cells. Cells with multisynaptic efferent connections to the motor-related cortical sites are located mainly in the lobules IV-VI of the cerebellar cortex (Kelly & Strick, 2003; Ramnani, 2006). They are directly connected to the main cerebellar output to the cortex - the dorsal dentate nucleus - specifically to the same region that contains the output to the SMA and the primary arm motor area (Kelly & Strick, 2003; Strick et al., 2009). Importantly, these projections are segregated from those to prefrontal areas both on the level of cerebellar lobules and dentate nucleus.

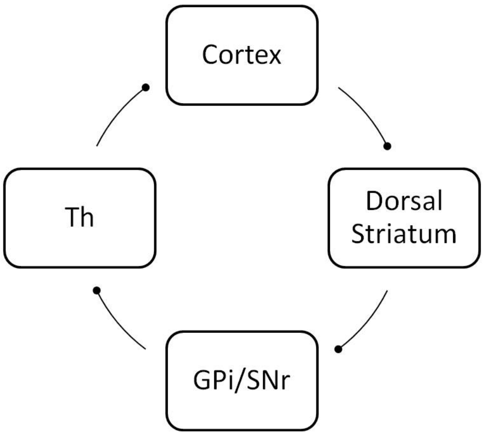

Figure 3.4.: *Schematic diagram of the multisynaptic basal-ganglia-thalamo-cortical circuit of the premotor cortex according to Nieuwenhuys et al. (2008) and McFarland & Haber (2000). CN, Cerebellar nuclei; PC, Purkinje cells; GPi, globus pallidus (capsual interna); SNr, substantia nigra; Th, thalamus*

3.1.3.3. Basal ganglia

The basal ganglia receive inputs from the cerebral cortex that first project to the striatum (caudate nucleus and putamen). The inputs go onward to the globus pallidus or substantia nigra, which in turn send signals back to the cerebral cortex via the thalamus (Fig. 3.4). There are multiple parallel loops, or circuits, in the corticostriatal system, each of which comprises a parent cerebral cortical area, including motor, association, or limbic cortex (Schmahmann & Pandya, 2008). The PMv is part of the the basal-ganglia thalamocortical loop (Nakano et al., 2000). This connection will be described in the following sections.

Efferents Although some projections from interconnected frontal cortical areas overlap, their primary projections remain segregated within the striatum. In the dorsal striatum, SMA efferents primarily target the central, dorsal putamen, while PMv efferents mainly target the ventral putamen (McFarland & Haber, 2000). A rostral-to caudal hierarchy has been proposed with regard to motor-cortical areas: While rostral areas primarily process cognitive aspects of motor control, caudal areas are more directly involved in movement execution. This hierarchy is mirrored in partly segregated cortico-striatal projections, which can also be observed within the PMv. Retrograde injections in the dorsolateral putamen show dense labeling in caudal motor areas such as M1, caudal PMv, and cingulate motor area (CMA), whereas ventral putamen and dorsolateral caudate injections labeled rostral PMv, PMd, CMA and pre-SMA (McFarland & Haber, 2000).

Afferents Output channels of the basal ganglia to the primary motor area and supplementary motor area appear to be topographically segregated from those to the lateral premotor cortex (Nakano et al., 2000). Strick (2004) demonstrated the ventrolateral globus pallidus (capsula interna) projection to the arm area of the PMv. PMv, as well as hand motor area, receive strong basal ganglia and cerebellar input via ventral lateral thalamic nucleus (Nakano et al., 2000). Findings indicate that ventral thalamic projections relay basal ganglia output to frontal cortical areas, but also provide direct feedback to the striatum[5].

Taken together, the above anatomical evidence indicates that the PMv may be an important node for auditory-motor integration. On the one hand, the PMv is structurally a region at the verge of the prefrontal cortex and a relay in the dorsal auditory stream in humans in contrast to non-human primates. On the other hand, the PMv has dense interconnections with other motor cortical regions: the SMA and the primary motor cortex. It modulates movements via efferent projections to the primary motor cortex and, directly, via projections to the spinal chord. Finally, this region is integrated into two cortico-subcortical loops, one formed with the lateral cerebellum and another with the dorsal striatum, which influence the output the PMv sends to other cortical areas and the corticospinal tract.

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[5] The latter thalamo-striatal feedback connection is not depicted in Fig. 3.4

3.2. Function

As a part of the dorsal auditory stream, comprising superior temporal gyrus (STG), sylvian parieto-temporal region and inferior frontal regions, the PMv has been shown to be a node for auditory-motor integration, specifically with regard to sequential auditory patterns like speech or music (Hickok & Poeppel, 2007; Zatorre et al., 2007; Rauschecker & Scott, 2009; Warren et al., 2005), in which temporal integration is critical. This is in contrast to the ventral auditory pathway that is functionally relevant for invariant auditory features and object identification (Zatorre et al., 2007, 2004; Rauschecker & Tian, 2000).

Although PMv in non-human primates and PMv in humans appears to have considerable differences in its anatomical connectivity, in particular to auditory regions in the superior temporal cortex, it is nevertheless essential to consider both sources of evidence on the function of this region. While imaging experiments provide information on functional properties of brain regions in humans with a resolution of typically above 3 mm^3, they area not capable of revealing, whether the same, partly overlapping or different neuronal populations are active during different tasks. In other words, it is not possible to infer precisely which types of neurons are activated by the tasks. It is particularly important to keep this in mind, when it comes to findings reporting ”mirror” neurons in the PMv exclusively based on hemodynamic activity (cf. for instance D'Ausilio (2009), Lahav et al. (2007))[6]. In contrast, intracortical recordings allow to map functional properties in the very same neuronal populations according to their participation in different tasks. Consequently, intracortical recordings in non-human primates represent a valuable source of information on a subset of basic auditory-motor integration functions of the PMv and are summarized below. Human neuroimaging, TMS and patient studies, however,

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[6] Until today no direct evidence of visuo-motor or audio-motor mirror neurons has been reported in humans in the PMv, Broca's area or adjacent frontal cortices by intracortical recordings.

will be confined to studies examining more complex functions of the PMv, namely perceptual timing, rhythmic sequence prediction and auditory-motor integration of rhythm.

3.2.1. Recording in non-human primates

Up to know there has been no account on neurons in the PMv in macaques that would suggest a functional tuning to auditory rhythm processing. This does not come as a surprise. In general, auditory responses are relatively rear in monkeys, which might partly be a consequence of reduced anatomical projections that connect superior temporal with inferior frontal cortices, as outlined above. Moreover, monkeys do not appear to synchronize their responses to rhythmic sequences. Nevertheless, several studies revealed a significance of this area in more general auditory-motor functions such as auditory localization, multisensory integration and attention to action-related sounds.

Graziano et al. (1999) reported neurons in the PMv of macaque monkeys to represent the auditory space surrounding the head. These neurons have spatial receptive fields that extend a limited distance outward from the head. In a follow-up study Graziano & Gandhi (2000) recorded multi-unit activity along the precentral gyrus of anesthetized monkeys. Auditory responsiveness was tested with a hand-held device that produced an approximately square-wave pulse at a distance of 20 cm. In addition, claps, voice, and the sound of gloved fingers rubbing against each other were tested. Auditory responses were rare and found in only two out of three tested monkeys. They were all reported in the upper-most part of the PMv, in so-called polysensory zone, which houses neurons that code for somatosensory (face, hand and partly arm), as well as visual stimulation. The authors suggested that the polysensory zone may contribute to the guidance of movement on the basis of tactile, visual and auditory signals.

Besides visuomotor ”mirror” neurons, audiovisual ”mirror” neurons have been found in the PMv (area F5) of macaques (Kohler et al., 2002; Keysers et al., 2003). These neurons discharge both when the animal performs a specific action and when it hears the related sound like paper ripping, peanut breaking etc. These neurons also discharge when the monkey observes the same action. Therefore, they represent actions independently of whether these actions are performed, heard or seen. Keysers and colleagues concluded that such neurons might represent a link to the evolution of speech in primates, since they are located in a putative homologue of Broca’s area, represent abstract action contents and process auditory information.

3.2.2. Neuroimaging

3.2.2.1. Perceptual timing

Although the PMv is still conceived as a motorcortical area, neuroimaging studies have repeatedly shown the PMv to be involved in perceptual timing tasks. These results have been revealed both in the visual and auditory modalities. The tasks can be subdivided into rhythms with (i) discrete event durations and (ii) sequences of event durations. While the former are usually tested within explicit and implicit time estimation paradigms, the latter involve tasks requiring the detection of timing deviants in a sequence of durations. Importantly, both tasks rely on temporal prediction.

Another feature that unites these tasks reported to yield activity in the PMv is the fact that the respective durations of single events, whether embedded or not embedded in sequences, is typically within a hundreds of milliseconds to seconds range, which is in line with the time range of repetitive movements, as outlined above. Such a correspondence already points to a role of the PMv in sensorimotor integration. Moreover, it corresponds to the notion that driving-plus-driven system entrainment is most evident when a driving rhythm has a rate that approximates the intrinsic period of a driven system (Drake et al., 2000).

Time estimation With regard to single interval durations Coull et al. (2004) demonstrated enhanced activity in the right frontal operculum that correlated with increased attention directed to the duration of a stimulus in contrast to its color. Data from the same group supported this finding by showing that a spatio-temporal visual task that required subjects to predict whether a braking car would eventually collide with a distant wall, enganges the left PMv comprising inferior BA 6 and extending into BA 44 (Coull et al., 2008).

Prediction of rhythmic sequences Both visual and auditory rhythmical sequence prediction has been consistently shown to activate the bilateral PMv within a serial prediction task (SPT) paradigm (Schubotz et al., 2000; Schubotz & von Cramon, 2003; Schubotz, 2007). Sequences used typically consist of chunks with two to four durations ranging from about 200 ms to 1800 ms repeated two to four times. The subjects' task is to attend to the order of the durations and to try to predict upcoming stimuli on that basis. To control for the subjects' engagement in the prediction process, a forced-choice task is implemented at the end of each trial where subjects have to indicate by button press whether or not the sequence unfolded as they predicted. As a control, target detection tasks or serial match-to-sample tasks are used to match perception, alertness, and response selection to the SPT, without a requirement for temporal prediction, i.e. the temporal relationship between consecutive stimuli is task-irrelevant in the control condition.

These rhythm tasks were found to correlate with a significant increase of metabolism in the inferior portion of the PMv (Schubotz et al., 2000; Schubotz & von Cramon, 2001b; Schubotz et al., 2003; Wolfensteller et al., 2007). Reported activation encompassed parts of Brodmann Area (BA) 6v1 and 6r1 (according to Amunts et al. (2010)), as well as BA 44. These activation patterns related to rhythm prediction were often shown to be bilateral and robust across all studies from the group. Importantly, activations in the inferior PMv for rhythm SPT overlapped with those during imagery, observation and execution of mouth movements and vocalization (Wolfensteller et al., 2007).

3.2.2.2. Auditory-motor integration of musical sequences

A variety of neuroimaging studies has been conducted to uncover auditory-motor integration of musical sequences (Zatorre et al., 2007). However, despite the position of the PMv in the dorsal auditory stream, its specific role in auditory-motor integration of rhythm is still under discussion.

Accordingly, while PMv has been reported in auditory-motor synchronization studies requiring finger tapping to isochronous cues, e.g. in Thaut (2003); Jancke et al. (2000), there is also conflicting evidence: Pollok et al. (2009) magnetic encephalography (MEG) study report PMv activity only during synchronization to visual, but not to auditory cues. Moreover, tapping to isochronous beats with increased metrical salience due to intensity modulation revealed enhanced activity in the PMd, as well as an enhanced functional connectivity between PMd and the auditory cortex (Chen et al., 2006). While the PMd increase may be explained by observed covariance between beat saliency and longer tap durations, i.e. by a movement related component, the enhanced interaction cannot be reconciled with such an interpretation.

Bengtsson et al. (2009) found the PMd, SMA, preSMA, and lateral cerebellum to be more active when participants listened to rhythm sequences compared to random sequences. However, isochonous contrasted to non-isochonous rhythms did not yield activity in the PMd, but in the frontal operculum adjacent to the PMv. In addition Chen et al. (2008) reported PMd activity during attention to rhythm both when subject did and did not anticipate the reproduction of these rhythms. This was reported in contrast to the PMv, which was recruited during perceptual processes that were coupled to action.

In musical pitch tasks, activity in the PMv has been shown to increase during tone sequences as a function of previous auditory-motor coupling (Lahav et al., 2007). In this fMRI study, non-musicians were trained to play a pitch sequence on a keyboard. When they subsequently attended to the trained melody, activity in this region increased together with PMd, Broca's area and inferior parietal sites when contrasted to equally familiar but motorically untrained melodies. Similar findings were revealed in a study by Bangert et al. (2006): Pianists versus non-musicians yielded strong activity increase in the PMv, PMd and superior temporal gyrus both during passive listening to short piano melodies and when pressing keys on a mute MRI-compliant piano keyboard. However, with regard to the contribution of the PMv, these findings contradict a study demonstrating PMd and preSMA activity to increase in pianists, when they attended to piano sounds (Baumann et al., 2007). Furthermore, melodic and harmonic discrimination has been shown to yield activity in regions of vocal-motor planning and production, including the PMv (Brown & Martinez, 2007).

Zatorre et al. (2007) proposed the ventral in contrast to the dorsal premotor subdivision to be active on attending to music for which one has an associated motor program, i.e. a direct auditory-motor transformation. In other words, he hypothesized that the PMv is involved in direct sound-to-movement mappings, whereas the PMd mediates the higher-order selection of movements based on information derived from a sensory cue. This distinction between direct and indirect auditory-motor interactions is in accordance with macaque studies on direct versus indirect sensorimotor transformations of visual sequences (Hoshi & Tanji, 2007), but stands in opposition to the habitual pragmatic event model (HAPEM, Schubotz (2007)), presented below. The HAPEM is in line with a somatotopic organization of the precentral gyrus insofar as it assumes that there is a gradient of transformation modes which self-induced movements and external stimuli can undergo. In contrast, the former account, differentiates the function of the two regions according to the motor significance of external stimuli.

Further findings shed light on the interaction of the lateral and medial premotor and subcortical systems during rhythm perception. An enhanced functional connectivity between activity in the superior PMv, SMA and putamen was revealed, when subjects indicated that they felt a regular beat rate in an auditory rhythmic sequence (Grahn & Rowe, 2009). In contrast to musical rhythms that exhibit externally paced beats which are emphasized by amplitude or pitch modulations, parts of the stimuli were rhythms, in which the beat had to be generated internally arising from the interval structure of the rhythms, being multiples or subdivisions of the beat. Functional MRI and Parkinson's disease patients studies suggest this process to draw on the SMA-basal-ganglia loop (Grahn & Brett, 2009, 2007). In accordance to Goldberg (1985), the enhanced interaction of the midline and lateral systems indicates that, in spite of the fact that PMv activity does not significantly increase during internally generated rhythms, it yet provides resources that enable an internal prediction of the underlying beat onset on the basis of externally paced events.

Results by Grahn & Brett (2009, 2007) correspond to the reported compensatory function of external cues in basal ganglia dysfunction: Musical material often exhibits continuous external cueing and it has been demonstrated to improve walking ability and speech in Parkinsons disease and stroke patients (McIntosh et al., 1997; Thaut et al., 2001).

Interestingly, attention to preferred or highly pleasurable musical stimuli have been reported to engage a subset of motor-related sites, such as supplementary motor area (SMA), cerebellum and Rolandic operculum (Blood & Zatorre, 2001; Koelsch et al., 2006). The rhythmic component of the musical material used in these studies may potentially explain activity boosts in motor-related regions on the basis of the tight link between auditory pulse and the motor system. However, so far, there has been no direct evidence suggesting a contribution of the motor system to the aesthetic appreciation of auditory rhythms.

3.2.3. Ventral premotor impairment

3.2.3.1. Lesion studies in macaques monkeys

Non-human primates do not exhibit vocal learning in the form of vocal imitation. However, monkey vocalizations can be acquired by conditioning. In squirrel monkeys, the PMv has been shown to be a part of the motorcortical pathway, which controls the patterning of learned in contrast to innate vocal utterances via the reticular formation (Jurgens, 2008). Lesion of the inferior PMv produced a detrimental effect on the control of acquired vocal utterances, but not on innate vocalizations in monkeys which are sub-served by a region in the anterior cingulate cortex (Jurgens, 2008).

3.2.3.2. Patient studies

Schubotz et al. (2004) tested performance on visual rhythm, object and position SPT in patients with ventral premotor lesions against age and gender matched controls, and compared their performance to that of patients with parietal and prefrontal lesions. Performance in rhythm and position SPT was impaired in premotor patients only. However, while the highest overlap of the premotor lesion was located in the

PMv, the lesions extended above the inferior frontal sulcus in some subjects. It thus cannot be excluded that superior PMv and PMd contributed to this effect. Note that the modality of stimulation, in this case, visual and not auditory, partly explains the impairment of rhythm SPT in patients with lesion in the superior PMv, since visual stimuli typically engage the superior PMv, whereas auditory stimuli tend to engage the inferior PMv (Schubotz & von Cramon, 2001a, 2003).

A damage to the PMv impairs certain types of vocalizations and speech. As suggested by lesion evidence in non-human primates described above, patients with lesions in the lower motor cortex and adjacent areas can produce emotional vocal utterances like moaning, crying and laughing, however, the production of learned vocal utterances, such as speaking and singing is disrupted, i.e. there is a loss of fine motor control over the phonatory apparatus (Jurgens & von Cramon, 1982). The lack of motor control over learned, but not over innate vocalizations suggests that the inferior PMv houses neuronal populations that enable a precise timing of vocal sequences. This is supported by evidence showing that adolescent and adult subjects with stuttering show a lower fractional anisotropy of white matter tracts underlying the PMv compared to healthy controls (Watkins et al., 2008), as well as volumetric differences in the Rolandic operculum and the adjacent pars opercularis (Foundas et al., 2001)[7]. Moreover, persistent stuttering is associated with mobilization of brain regions contralateral to the structural anomalies for compensation attempt (Kell et al., 2009). However, since stuttering has also been attributed to basal ganglia dysfunction (Alm, 2004), it may be that this anatomical and functional anomalies in the PMv are compensatory rather than causal.

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[7] The reported structural abnormalities of white matter tracts underlying the lateral ventral premotor area may partly arise due to an altered gyrification of frontal and temporo-parietal areas in subjects with stuttering (Foundas, et al. 2001).

3.2.3.3. Transcranial magnetic stimulation (TMS) studies

Malcolm et al. (2008) used repetitive TMS (rTMS) to test the casual contribution of the left PMv to synchronization with a metronome beat. In contrast to rTMS over the superior temporo-parietal cortex, rTMS over the left PMv did not show a significant effect on auditory-motor synchronization. However, the authors assessed the absolute tap-to-beat asynchrony and not the accuracy of synchronization, which can be conceived to reflect the accuracy of the internal forward model. While an increased tap-to-beat-asynchrony may still be very consistent, and therefore accurate across taps, it is the variability of tap-to-beat asynchrony that reflects synchronization accuracy (Repp, 2005). Furthermore, tapping to a metronome click requires only minimal attention to the auditory modality. It is therefore possible that the synchronization processes required in the present context differ substantially from auditory-motor integration of a beat in a musical context, i.e. in the presence of other auditory cues. Finally, it is possible that the inhibitory stimulation of the left PMv triggered activity increases in the homologous right PMv that effectively compensated for the dysfunction in the stimulated area.

It is important to note that other regions have been reported to be causally related to right hand tapping synchronization. Olmo et al. (2007) report an increase of the variability of the intertap interval after rTMS of the cerebellum ipsilateral to the moving hand. Importantly, this was found only for movements in the subseconds, but not in the seconds range that were made while subjects were synchronizing with an auditory cue. There was no effect on the continuation phase or on synchronization with a visual cue. Similar results were revealed after stimulation over the contralateral dorsal premotor cortex.

Meister et al. (2007) showed that rTMS over a region on the border between PMv and PMd can impair speech-related processing - phonetic discrimination of

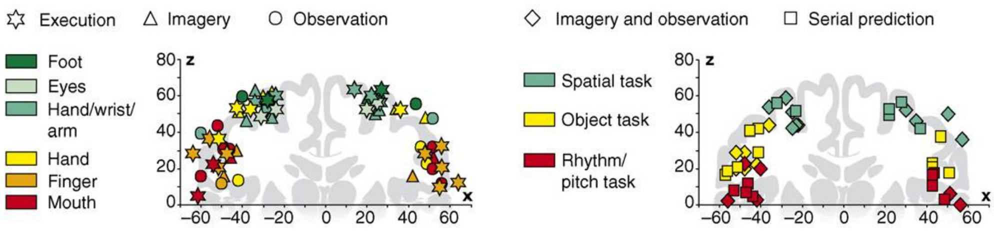

Figure 3.5.: *Habitual Pragmatic Event Map (HAPEM) as adapted from Schubotz & von Cramon (2003); Schubotz (2007). The meta-analysis on motor and cognitive activations in the lateral premotor cortex (Schubotz & von Cramon, 2003) suggests that prediction-related activity is structured according to different motor effectors.*

voiceless stop consonants in single syllables, but not a color discrimination control task. This finding suggests that a perceptual processing of speech sounds draws on resources in a motor-related region.

3.2.4. "Habitual Pragmatic Event Map" (HAPEM)

The recruitment of a vocalization-related premotor area during perceptual timing and auditory-motor synchronization advocates the notion of the HAPEM (Schubotz, 2007). The latter provides a theoretical explanation for the observed neural overlap of motor and non-motor cognitive functions. The HAPEM framework claims that activity in the lateral premotor cortex is structured according to different transformation modes such as *rotation*, *deformation*, or *acceleration*, rather than to motor effectors per se. Both self-induced and observed events can undergo these transformations. The sub-regions of the premotor cortex are best adapted to their motor output in terms of the above transformation modes (3.5).

Accordingly, the dorsal subdivision of the lateral premotor cortex is involved in arm movement and observation, as well as in perceptual tasks that require attention to space, because both events amount to a translation of position, i.e. rotation. Likewise, the midline portion of the premotor cortex is active during hand or mouth movements, as well as object transformation, because it is tuned to deformation, expansion and contraction. Finally, the inferior ventral premotor region has been associated with vocalization, as well as with attention to rhythm (Schubotz & von Cramon, 2001b; Schubotz et al., 2003; Thaut, 2003; Wolfensteller et al., 2007) and melody/harmony (Brown & Martinez, 2007; Meyer et al., 2004; Schubotz & von Cramon, 2002b), because it is tuned to ac-/deceleration and pitch rising/falling. These changes are at the heart of both vocalization and articulation. Similarly, external temporal events such as musical rhythms and especially the tempo of a musical rhythm involve changes defined by ac-/deceleration. Therefore, as established for the domain of action performance, imagery, and observation, motor networks may be considered to provide forward models that enable attention to change beyond the action domain (Grush, 2004; Wolpert & Flanagan, 2001), such as auditory rhythm. Importantly, premotor cortex activation amounts only to a fraction of action, since an integral part of movement and movement imagery - real or predicted interoceptive information such as proprioception - is missing. The reported PMv activity in perceptual rhythm tasks is thus a fraction of action representation. It exploits only the vocal and articulatory circuit, i.e. a subset of sensorimotor neurons in the areas controlling vocal and articulatory actions (Schubotz, 2007).

Note that this framework does not *a priori* lend support to the notion of ”embodiment” and ”embodied simulation” with regard to musical rhythm perception (Leman, 2008), a term that suggests either movement or movement imagery and therefore an interoceptive component. Despite the involvement of a motor-related region in perceptual rhythm tasks, as well as evidence for a tight behavioral coupling between musical rhythm and movement, this term should be applicable to auditory-motor coupling, but not to perceptual comprehension of sound sequences in general. This is in contrast to the term ”sensorimotor simulation” which will be used parsimoniously in the present work, merely referring to an auditory-motor fraction of forward models for motor control (Grush, 2004; Schubotz, 2007).

4. Questions and hypotheses

The following sections provide a brief summary of the main objectives and hypotheses that are addressed in *Experiments 1*, *2* and *3*. Note that each introductory section of the respective experiment accommodates a more in-depth outline of these hypotheses by relating them to the theoretical part of the present work.

4.1. PMv and auditory rhythmic preference

Humans tend to tune in to a musical pulse by head nodding, toe tapping or humming, when they like a musical piece. Behavioral studies confirmed a tight link between auditory rhythm preference and movement. Moreover, preferred musical stimuli enhance BOLD activity in a subset of motor-related sites. A the same time, activity increase in a motor-related region in the dorsal auditory stream - the PMv - has been frequently reported in predictive rhythm and timing tasks requiring either attention or synchronization of single intervals or interval sequences. The latter suggests mechanisms of internal simulation via forward models in these tasks. Despite the variety of studies investigating the association of rhythm and the motor system, the neural mechanisms mediating auditory rhythm preference remain unknown.

The following hypotheses (*H1-H4*) refer to the contribution of the PMv in perceptual rhythmic preference:

H1: Attention to individually preferred rhythms is accompanied by activity in the PMv (Experiment 1).

On the basis of the behavioral link between rhythmic preferences and movement, musical rhythms with an individually preferred beat rate should reveal a greater activity increase in the PMv when compared to those with a not preferred beat rate. This effect of preference should be specific for beat rate, i.e. an event rate around 2 Hz that corresponds to the frequency of repetitive movements. A boost in PMv activity should not be associated with the preference of a non-rhythmic property of the musical rhythms, such as instrumental timbre.

H2: Activity increase in the PMv during preferred rhythms corresponds to activity increase during a perceptual rhythm task (Experiment 1).

If *H1* is correct and increased activity in the PMv is related to an internal simulation of the beat rate, it should match the activity increase associated with a beat rate identification task.

H3: Inhibitory stimulation of the PMv interferes with rhythmic preference strength (Experiment 2).

While an activity increase during preferred beat rate advocates a contribution of the neural measure and behavioral state, it may still reflect a co-activation with other causally relevant regions. Interference with its normal activity, however, provides additional support for a causal contribution of this region to a task (*Experiment 2*). Accordingly, inhibitory interference with PMv activity should yield a transient detrimental effect on beat rate preference.

H4: Effect of PMv stimulation on rhythmic preference strength can be explained by performance in an auditory rhythm task (Experiment 2).

If both *H2* and *H3* are supported and auditory beat rate preference can be explained by the same neural mechanisms as yielded by an auditory rhythm task, the beat rate preference strength should covary with the effect of PMv stimulation of the beat rate identification task.

4.2. PMv and auditory-motor synchronization

Neuroimaging studies revealed PMv in auditory-motor timing tasks. Although the PMv in the left hemisphere has been shown to be causally relevant for speech, which like music requires precise sequential timing, no evidence has been provided for a causal role of this cortical region in auditory-motor timing so far. Moreover, it remains unknown which degenerate set of regions can compensate its disruption in auditory-motor timing. The following hypothesis *H5-H7* refer to the causal role of the left PMv in auditory-motor synchronization to a musical beat.

H5: Inhibitory stimulation of the PMv interferes with effector-independent synchronization accuracy (Experiment 3).
In case of a causal contribution of the PMv to general auditory-motor timing, results should reveal an effect of PMv stimulation in one hemisphere on at least two motor effectors. An experiment involving both right and left finger tapping to a beat of musical rhythms should demonstrated the effect of PMv stimulation of synchronization accuracy.

H6: Inhibitory stimulation of the PMv causes activity increase in interconnected areas during auditory-motor synchronization (Experiment 3).
Short-term functional reorganization after PMv disruption should elevate activity in areas interconnected to the PMv during auditory-motor synchronization. Specifically, the homologous PMv in the hemisphere contralateral to the stimulated should reveal an activity boost due to decreased transcallosal inhibition.

H7: A subset of compensatory mechanisms help to preserve synchronization ac-

curacy after inhibitory stimulation of the PMv (Experiment 3).

If *H6* is confirmed and interconnected regions can take over the function of the PMv, than neuroimaging should reveal an inverse correlation between activity in these areas and the behavioral effect of PMv stimulation: The higher activity increases in these regions, the smaller should the effect of left PMv stimulation be across subjects.

Part II.

Experimental studies

5. Methods

The current chapter provides a brief introduction to the methods used in the experimental work of the present thesis, namely functional magnetic resonance imaging (fMRI), repetitive transcranial magnetic stimulation (rTMS) and the combination of these two techniques (offline rTMS-fMRI).

5.1. Functional Magnetic Resonance Imaging (fMRI)

In humans fMRI can be used to assess activity in the brain during specific experimental tasks and states. Important empirical observations can be made with regard to how consistently activity increases in and interactions between certain brain regions accompany certain tasks. The dependence of fMRI on blood oxygenation renders this method particularly suitable for functional imaging of the human brain. In contrast to positron emission tomography (PET), fMRI is non-invasive, i.e. it does not involve the injection of radioactive tracers into the bloodstream. In addition, it offers a better temporal (in the order of seconds) then PET and a better spatial resolution (1 mm) compared to both PET and other neuroimaging techniques like electro- and magnetoencephalography (EEG and MEG).

5.1.1. Physical basics

Most biological tissue is water-based (70-90 %) and the amount of water in different tissue types varies. The single protons of hydrogen nuclei that are found in water molecules (H_2O) in the body have a quantum mechanical property called spin, which can be most easily thought of as a tiny spinning magnet. Note that many atomic nuclei possess this property, however, nuclei like the water and fat protons in biological tissues dominate the signals measured in conventional MRI.

Normally spins are randomly oriented, facing different directions. When an external magnetic field is applied, a small fraction of the spins orient themselves with the magnetic field, i.e. they start to precess around the axis of the magnetic field according to the so-called Larmor frequency, which is related to the field through the gyromagnetic ratio (Logothetis, 2008). The strength of the applied magnetic field is measured in Tesla (T). Typically MRI scanners used for basic and clinical purposes have field strength between 1.5 T and 3 T, whereas the Earth's magnetic field is in the order of 0.0001 T. The magnetic field is applied constantly during the scanning process. When a radio frequency (RF) field rotating synchronously with the precessing spins is applied, the orientation of the spins rotates by 90 degrees to their original orientation: the longitudinal magnetization is converted to transverse magnetization. Moreover, the spins precess in phase with each other. As long as the spins are not completely dephased and have not turned back to their original orientation, we can receive a signal from the spins. Since this change in orientation and phase happens only when the carrier frequency of the RF pulse is equal to the Larmor frequency, the term *magnetic resonance* has been coined. The transverse magnetization decays as a result of processes known as relaxation. Variations in the rate at which the spins return back to the original state following the RF pulse (the relaxation rate) can be used to distinguish between different types of biological tissue, since these reflect the non-uniform distribution of water molecules within them. These differences form the basis of an image contrast. Importantly, there are different kinds of relaxation processes, each reflecting different interactions of the spins with their environment or with other spins: The longitudinal relaxation time T1 is the time of recovery of longitudinal magnetization after an RF pulse. The transversal relaxation time T2/T2* is the time of decay of transversal magnetization due to the loss of phase coherence between spins (T2) and changes in local field inhomogeneities (T2*). By varying the time periods between RF pulses (time repetition; TR) and the time between pulse and begin of data acquisition (echo time; TE), it is possible to create pulse sequences which are sensitive to different tissue types, such as white or gray matter.

Functional magnetic resonance imaging (fMRI) reflects the dependence of T2*-weighted contrasts on the amount of blood oxygenation as first discovered by Ogawa in 1990 (Ogawa et al., 1990): Deoxygenated in contrast to oxygenated hemoglobin is paramagnetic and, therefore, induces inhomogeneities into the local magnetic field. The more deoxygenated hemoglobin is in the blood, the faster the decrease in relaxation time (T2*) and the lower the blood oxygen level dependent (BOLD) signal.

5.1.2. Physiological basics

Communication within and between neurons (e.g. ion transportation and neurotransmitter metabolism) requires energy, provided by oxygen and glucose. When neurons consume oxygen they convert oxyhemoglobin to paramagnetic deoxyhemoglobin that introduces distortions into the magnetic field. As neurons do not store oxygen and little glucose internally, increased neuronal activity requires more oxygen and glucose to be rapidly delivered through blood stream. Thus, when the metabolic activity of neurons increases, the blood supply to that region increases to meet this demand. More specifically, the origin of the fMRI signal (BOLD) is an oversupply of freshly oxygenated blood that leads to a signal increase in the activated areas.

What neural activity does the BOLD signal reflect? The exact relationship between neural activity and BOLD signal is very complex and, despite the prevalent use of fMRI in clinical and basic research, still in parts unclear (Goense & Logothetis, 2010). However, studies that utilized simultaneous fMRI and electrophysiology in anaesthetized and awake monkeys repeatedly demonstrated that the fMRI response is best correlated with the local input and local processing rather then the output of a neural circuit (Logothetis et al., 2001; Goense & Logothetis, 2008). This means that fMRI signal reflects the synaptic activity driving neuronal assemblies rather than the neuronal firing patterns produced by the neurons.

The changes in the BOLD signal over time that are coupled to an event are described by the hemodynamic response function (HRF). The poststimulus HRF has roughly three phases that have been associated with different physiological mechanisms:

1. *Initial dip*: Neurons consume oxygen and thus there is a rise in the amount of deoxyhemoglobin, which in turn results in a reduction of the BOLD signal.
2. *Overcompensation*: The blood flow to the region increases, due to an increased consumption of oxygen. It increases to the degree that overcompensates for the demand of oxygen at this region.
3. *Undershoot*: The blood flow and oxygen consumption dip before returning to their original level. Its physiological basis is still under debate. Recent evidence extends the notion of a passive vascular effect, suggesting that the poststimulus undershoot is a neurally driven component (Sadaghiani et al.,

2009).

The HRF depends on such properties as the intensity and length of stimulation and differs significantly between individuals and different regions within individuals (Aguirre et al., 1997). It is important to emphasize that the brain is always physiologically active. It consumes 20% of the body's oxygen uptake, despite the fact that it is only 2% of body weight (Gusnard & Raichle, 2001). The majority of its large energy budget is devoted to what has been called the resting state, i.e. task-independent activity. Relative to this very high rate of basic metabolism, the amount dedicated to changes of brain activity during different task-related states, that are often the focus of fMRI studies, is comparably small. A major factor in the success in of activation studies with BOLD fMRI can be attributed to the development of statistical data processing (Friston et al., 1995b), which enabled to evaluate the significance of these fairly weak task-related relative to task-unrelated activity. These small relative task-related BOLD signal changes are the basis for the fMRI studies presented in the current thesis.

5.2. Repetitive Transcranial Magnetic Stimulation (rTMS)

With fMRI it is possible to identify regions, which activity systematically accompany certain behavioral states. To address the question whether activity in a region causally contributes to a certain behavior it is necessary to interfere with normal activity in this region. Transcranial Magnetic Stimulation (TMS) allows to do so non-invasively, that is without directly penetrating the brain surface, as during electric intracranial stimulation, as outlined below. Specific TMS protocols can be used to transiently interfere with local brain activity to observe their immediate or longer lasting impact on behavior. By careful application, TMS can be used to transiently recreate the deficits seen in some neuropsychological patients - a ”virtual” lesion, or can be used to create deficits that are rarely, if ever, obtained in neurological patients (Cowey & Walsh, 2000).

5.2.1. Physical basics

TMS is based on electromagnetic induction, a principle first discovered by Michael Faraday in 1831. In his experiments he could show that a temporally and spatially changing magnetic field induces an electric flow in a nearby conductor. Thus, if an electrical current is passed through one coil, the current in the first coil produces a magnetic field that in turn causes current to flow in the second coil. If the TMS coil is held over a subjects head,that second coil is the brain tissue: The magnetic field penetrates scalp and skull, and induces an electric field in the brain. Accordingly, the main action chain of TMS is as follows: the TMS machine delivers a large current in a short period of time, the current in the TMS coil then produces a magnetic field and the latter, if changing rapidly enough, will induce an electric field sufficient to stimulate neurons or change the resting membrane potentials in the underlying cortex. The magnitude of the induced electric field is proportional to the time rate of change of the magnetic field, which in the case of TMS is determined by the rate of change of the current in the coil.

The geometrical configuration of the coil influences the focality of the stimulation. In a round coil the magnetic field has its maximum at the center of the coil, whereas the induced electrical field is maximal directly under the coil ring and minimal at the central part. The stimulation with a round coil is thus not useful when a functional involvement of a circumscribed area is of interest. Thus, in most studies of cognitive function the TMS coil will have a figure-of-eight shape, i.e. consisting

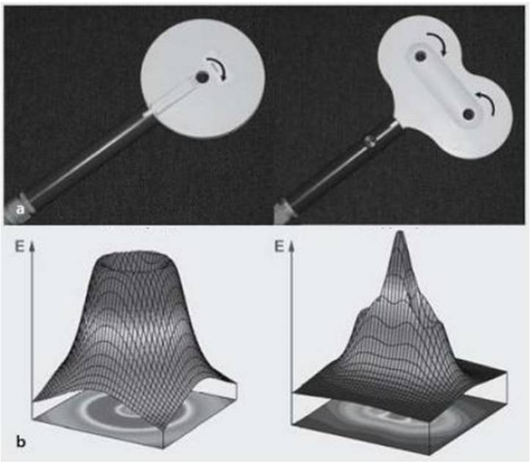

Figure 5.1.: *Round and figure-of-eight TMS coils and their induced electric field. Adapted from Weyh & Siebner (2007)*

of two connected round coils. This coil type induces a maximum electrical field with a peak under the intersection of the two windings (Ren et al., 1995; Weyh & Siebner, 2007).

The stimulators and coils develop about 1.5-2.0 Tesla (T) at the face of the coil, produce currents changing at rates up to 170 A/µs and induce electric fields in the cortex of up to about 150 V/m (Rossi et al., 2009) .

5.2.2. Physiological basics

The induced electric field can be of sufficient magnitude and density to depolarize neurons, and when TMS pulses are applied repetitively they can modulate cortical excitability, decreasing or increasing it, depending on the parameters of stimulation, even beyond the duration of the train of stimulation (Rossi et al., 2009). In short, TMS can be used to induce a transient interruption of normal brain activity in a relatively restricted area of the brain. However, the cortical microarchitecture is complex and differs across regions. Potential anatomical structures for TMS are axons of pyramidal axons which run perpendicular to the cortical surface. The flow of ions brought about by the electric field induced in the brain alters the electric charge stored on both sides of cell membranes, depolarizing or hyperpolarizing neurons. The existence of passive ion channels renders the membrane permeable to these ions: an increased membrane conductance decreases the amplitude of the change in membrane potential due to the induced electric field and decreases the time constant that characterizes the leakage of the induced charge. Experimental evidence and theoretical calculations reviewed by Siebner & Ziemann (2007) suggest that stimulation occurs at a lower threshold where axons terminate (e.g. a synapse), or bend sharply, in the relatively uniform electric field induced by the TMS stimulation coil. Axons with larger length constants, and hence larger diameters, are expected to be stimulated at lower stimulus intensity.

5.3. Combination of rTMS and fMRI

Although subcortical, as well as cortical regions of the brain exhibit functional specializations, the brain circuitry has an in-build degeneracy Friston & Price (2003). When one region or pathway is damaged, others might be able to compensate for the loss, at least in parts (O'Shea et al., 2007; Chollet et al., 1991; Kell et al., 2009). The combination of rTMS and subsequent fMRI is potentially capable of revealing these transient compensatory mechanisms.

rTMS-fMRI presents several advantages over patient studies. It enables experimental control over the focality, onset, and duration of neural interference. Moreover, it is not confounded by typically great variations across patients with regard to lesion onset, size or location, symptom severity, diaschisis, i.e. functional damage to connected areas and post-lesion plasticity. Further, it provided information about the immediate impact of neural disruption on activity in connected brain regions. Finally, healthy individuals act as their own controls, thus providing more closely matched baseline data than might be possible with patients.

However, the combination of these techniques has several limitations. There is still only limited insight on the influence of rTMS on neurophysiological and BOLD signals (Bestmann, 2008), although neural changes seem to be well reflected by hemodynamic signals (Allen et al., 2007). Moreover, since the perturbation of brain activity is very mild, the compensatory activity is transient, and may reveal a complex dynamic progression over time.

In addition, there are also several technical difficulties that have to be solved. The experimenter has to ensure that the interval between the end of rTMS and the beginning of the fMRI sequence does not exceed more than 4-5 minutes, since the behavioral effect may be detectable during the first minutes following the end of stimulation and cease over time (O'Shea et al., 2007); in addition short-term reorganization mechanisms may be lost. Thus, a fast transition of the subjects from the laboratory in which rTMS is performed to the scanner is essential. Here it is important to ensure a low variance of the interval across subjects. Finally, subject's movement and verbal interaction between the experimenter and the subject during this period should be minimized as much as possible, since these events can introduce noise or potentially mitigate the influence of rTMS on neural function.

6. Experiment 1. H1-H2. PMv and auditory rhythmic preference (fMRI)

6.1. Introduction

When listening to music that appeals to us, we often feel an immediate urge to tune in by head nodding, toe tapping or humming. It has been shown that complex musical stimuli inducing pleasurable responses enhance BOLD activity in a subset of motor-related sites - the supplementary motor area (SMA), the cerebellum and the Rolandic operculum (Blood & Zatorre, 2001; Koelsch et al., 2006). However, it remains uncertain whether these preference-associated activations can be induced by preferred rhythm alone, a component of music considered to be most fundamental with respect to linking sound to movement (Cross, 2001; Janata & Grafton, 2003; Thaut et al., 1999).

The motor system has been found to be recruited during attention to auditory and visual rhythm (Bengtsson et al., 2009; Chen et al., 2008; Coull et al., 2004; Grahn & Brett, 2007; Platel et al., 1997; Schubotz et al., 2000; Wolfensteller et al., 2007). Typically, motor-related areas are engaged by perceptual input in tasks that require attention to events of a subseconds duration such as a musical beat frequency, which corresponds to the time-range of voluntary movements (Lewis & Miall, 2003; Moelants, 2003). Within this motor network, the lateral premotor component has been specifically attributed to implicit perceptual timing of stimuli with a predictable temporal structure (Coull & Nobre, 2008). Studies report especially the ventral-most portion of the premotor cortex (PMv) for perceptual rhythm tasks (Schubotz & von Cramon, 2001b; Schubotz et al., 2003), an area that also corresponds to vocal imagery (Kleber et al., 2007; Riecker et al., 2000; Wolfensteller et al., 2007). This led to the assumption that PMv provides a common platform for attention to rhythmic structure, both perceived or produced (Schubotz, 2007). To explain the above convergence between motor and perceptual functions, the computational perspective offered the notion of sensorimotor simulation via internal forward models (Grush, 2004; Schubotz, 2007; Wolpert & Flanagan, 2001). These simulations serve to predict future motor, as well as perceptual states based on established sensorimotor representation of previous event templates such as rhythmical patterns in perceptual rhythm tasks. Although suggested by tuning-in behavior such as head nodding, toe tapping or humming to the music that appeals to us, it is an open question, whether the aesthetic appreciation of rhythms is positively correlated with such sensorimotor simulation.

In *Experiment 1* (Kornysheva et al., 2010), systematically controlled rhythmic musical patterns were used to test the hypothesis that activity in the motor system is particularly enhanced when subjects aesthetically appreciate musical rhythms. More specifically, the aim was to clarify whether activity enhancement for preferred musical rhythms can be traced back to preferred beat frequency, i.e., tempo.[1]. Tempo was expected to be the most important time-related property influencing the

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[1] The terms *beat rate*, *beat frequency* and *tempo* are used interchangeably to refer to the frequency of events occurring around 2 Hz.

subjects' preferences (i) due to its prominent role in auditory rhythm perception (Baruch & Drake, 1997; Bella et al., 2001; Drake et al., 2000; Trainor et al., 2004), and (ii) since it provides the underlying pulse, a beat, people tune in to when listening to music, i.e., it often triggers sensorimotor coupling (Chen et al., 2006; Drake et al., 2000; Fraisse, 1982; Large, 2000; Moelants, 2002, 2003; van Noorden & Moelants, 1999). To this end, brain data was modeled on the basis of individual judgment analyses including all constituents of the musical rhythms as predictors for the subjects' aesthetic judgments. Besides tempo, traits such as beat grouping (measure), beat subdivision, non-isochronous repetitive patterns and instrumental timbre[2] that a musical rhythm typically contains, were varied orthogonally.

In addition, to determine whether the hypothesized activity increase in motor-related areas during preferred tempo can be explained by enhanced sensorimotor simulation essential in a perceptual rhythm task, a tempo judgment condition was employed besides an aesthetic judgment condition. The subjects were asked to decide whether a musical rhythm is fast or not. In line with the notion of sensorimotor-driven forward models and the evidence for the involvement of motor-related areas in perceptual rhythm tasks, it was assumed that the tempo judgment task required enhanced sensorimotor simulation. Accordingly, to identify the tempo of an incoming auditory rhythm the subjects had to map an external beat frequency on their audiomotor representation of a template established on the basis of previous rhythms. Thus, the tempo judgment condition served as a control to determine whether the hypothesized activity increase in motor-related areas during preferred tempo can be explained by enhanced sensorimotor simulation. Additionally, the tempo judgment condition was used to ensure that the aesthetic judgments engaged the subjects in an evaluative in contrast to a tempo identification task.

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[2] The terms *timbre*, *instrument type* and *instrumental timbre* are used interchangeably to refer to the spectral configuration of sound stimuli.

6.2. Methods

6.2.1. Participants

Eighteen right-handed healthy volunteers (11 female, mean age 25.1 years, range 22-29 years) participated in the study. One additional participant had to be excluded due to inadequate behavioral performance (compare results section). All subjects received regular musical education at school which comprises singing melodies to a piano accompaniment, basic ensemble performance, the acquisition of elementary theoretical knowledge about Western musical harmony and rhythm, as well as about the general principles of musical notation, but no professional musical training. Six subjects received additional instrumental training or attended a choir for 1 to 13 years (mean: 6.1 years, SD: 5.4 years), but only three reported musical activities of 4 to 5 hours per week at the time of their participation in the experiment. To ensure that the stimulus material elicited appreciation in all participants, the subjects were preselected on the basis of a behavioral test, in which they were exposed to the stimulus material used in the current experiment. When asked how much they enjoyed the test, all 18 participants of the present fMRI-experiment indicated at least 5 on a 7-point rating scale ranging from ”not at all” to ”very much”. After being informed about the potential risks and screened by a physician of the institution (Max Planck Institute for Cognitive and Brain Sciences, Leipzig), subjects gave informed consent before participating. The experimental standards were approved by the local ethics committee of the University of Leipzig. Data were handled anonymously.

6.2.2. Stimuli and Tasks

Subjects were presented with auditory musical rhythms. The rhythm stimuli were constructed of drum sounds generated with the Microsoft Software Wavetable Synthesizer (GM drum map). The stimuli had five properties, each property varying on two or three levels respectively: tempo (slow, middle, fast; i.e. 600ms, 500ms, 400ms inter-onset-interval of beats corresponding to the beat frequencies: 1.7 Hz, 2 Hz, 2.5 Hz or 100, 120 and 150 beats per minute (BPM); quarter notes in musical notation), measure or beat grouping (3, 4, 5 beats; 3/4, 4/4, 5/4 meter in musical notation), beat subdivision (3, 4, 5 elements per beat; eighths note triplet, four sixteenth notes and sixteenth note quintuplet in musical notation), rhythmic figure (long interval - short interval, short interval - long interval; dotted note and syncopation in musical notation) and instrument type (”bongo”: predominantly wooden drum instruments; ”rock”: predominantly metal drum instruments; two versions each) (cf. 6.1, upper part).

The latter property was not time-related and was introduced to increase the variety of the stimulus material. The tempo (beat frequency) varied within the range of the preferred ”tempo-octave” of contemporary dance music (Moelants, 2003; van Noorden & Moelants, 1999). The rhythm stimuli appeared in all 216 possible combinations, e.g. the rhythmic figure ”long interval - short interval” occurred in all tempi, measure types, beat subdivisions, instrument types and instrument versions (cf. Supplementary material; Stimulus examples). Each combination of property levels was presented only once in the experiment, i.e., there were no stimulus repetitions.

Similar to the paradigm introduced by Jacobsen et al. (2006) in the context of aesthetic and symmetry judgments of abstract visual patterns, the stimulus material was used for aesthetic (AJ) and tempo (TJ) judgment conditions (cf. 6.1, lower

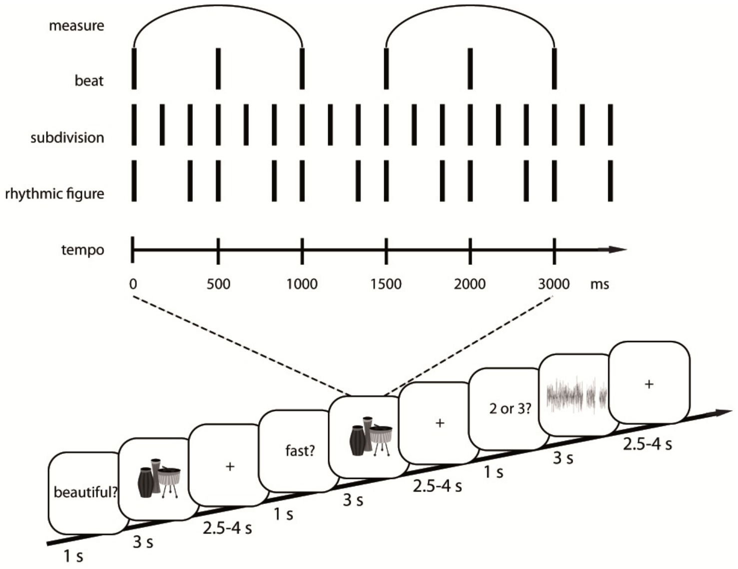


Figure 6.1.: *Structural elements of a musical rhythm and an exemplary trial sequence of both judgment tasks and the control condition. The rhythmical structure of a musical rhythm was determined by tempo (beat rate), measure (the grouping of beats), beat subdivision (elements per beat) and rhythmic figure. Additionally, instrument type was introduced to increase variety in the stimulus material. The depicted rhythm example schematically displays a middle tempo with three beats per measure, three elements per beat and a repetitive rhythmic figure containing a long, followed by a short interval. A variable jitter time of 2.5-4 s was followed by a task cue (1 s) and an auditory stimulus presented for 3 s. Participants were asked to press the selected response button when they had decided but still while the sound was presented. They were asked to decide whether or not the presented musical rhythm was beautiful (aesthetic judgment) or fast (tempo judgment); in the control condition, they were asked to press the left button if a white noise was interrupted by two silent gaps and the left button for three silent gaps.*

part). In a forced choice paradigm, participants were instructed to attend to the presented stimuli and to decide whether or not the presented stimulus was beautiful (aesthetic judgment) or fast (tempo judgment). The subjects were asked to judge the stimuli with regard to previous stimuli in the experiment. They were instructed to press the selected response button when they had decided while the rhythm was presented.

In German, the word ”beautiful” - ”schön” - also means ”nice” and ”pleasant”. Thus, the judgments ”beautiful” and ”not beautiful” was chosen to assess each subject’s liking of the rhythms. However, to ensure the correspondence between the judgment ”beautiful” and liking in the current experiment, the subjects were asked to indicate on a scale between -3 (”do not agree”) and +3 (”agree”) how strongly they consent to the statements that they (i) like and (ii) do not like musical rhythms which they judge as beautiful in a post-experimental interview. Results support that the judgment ”beautiful” was strongly coupled to liking (mean consent rating (N = 16): +2.4; 0.2 SE) in contrast to not liking (mean consent rating (N = 16): -2.7; 0.2 SE).

The temporal judgment task required dichotomous judgments on non-dichotomous features, just as the aesthetic judgment task, yet continuous attention to beat frequency for the identification of tempo. Additionally, a more basic control condition (CC) intermixed with the experimental trials was designed to monitor the subject’s overall attention, in which they were presented white noise stimuli that were interrupted by two or three silent gaps of 50ms. They were asked to press the left button for two and the right button for three interruptions. All stimuli were normalized in intensity level using root mean square (RMS).

Each trial (8 s) started with a cue (1 s), indicating whether to perform an aesthetic judgment (”beautiful?”), tempo judgment (”fast?”) or control condition task

(”2 or 3?”), followed by the stimulus (3 s) and a fixation phase (2.5-4 s), which length depended on the variable jitter times (0, 500, 1000 or 1500 ms) that were inserted between the trials to enhance the temporal resolution of the BOLD response. The duration of the stimulus was set to 3 s, i.e. approximately 1 s after the average RT, which was identified by preceding pilot testing. Altogether, 300 trials were presented: 108 in the AJ, 108 in the TJ, 54 in CC, as well as 30 empty trials (resting condition; RC), which were intermixed with the experimental trials. Each judgment condition was assigned 108 of 216 rhythm stimuli, the temporal factors (tempo, measure, beat subdivision and rhythmic figure) counterbalanced across conditions and the two instrument versions of ”bongo” and ”rock” counterbalanced across subjects. Instrument type ”bongo” and ”rock” were equally distributed across both judgment tasks. Each judgment task could occur maximally three times in a row. CC trials did not occur in a row. The frequency of all conditions, as well as all tempo types (slow, middle, fast) were equally distributed across sub-blocks of 100 trials. Moreover, all trial transitions between the two judgment conditions were counterbalanced across the session. 16 different trial randomizations matching the above criteria were used for 18 subjects.

To ensure the subjects became familiarized with the task and the musical rhythms as a point of reference for their preference and tempo judgments, a training containing 30 example trials (12 trials AJ, 12 trials TJ, 4 trials CC, 2 trials RC), which were randomly chosen from the pool of stimuli for each subject and counterbalanced for tempo type, was presented prior to the experimental session.

6.2.3. MRI Data acquisition

Imaging was performed at a 3 T scanner (Siemens TRIO, Erlangen, Germany) equipped with a standard birdcage head coil. Participants were placed on the scanner bed in a supine position with their right index and middle fingers positioned on the appropriate response buttons of a response box. To prevent postural adjustments, the participants' arms and hands were carefully stabilized by tape. In addition, form-fitting cushions were utilized to prevent head, arm and hand movements. Rhythms were presented over SereneSound Digital audio headphones with 30dB headset gradient noise attenuation. Further attenuation was achieved with insert earplugs rated to attenuate scanner noise by approximately 38 dB. Thirty axial slices (192 mm field of view, 64 x 64 pixel matrix, 4 mm thickness; 1 mm spacing, in-plane resolution of 3 x 3 mm) positioned parallel to the bicomissural plane (AC-PC) covering the whole brain were acquired using a single-shot gradient echo-planar imaging (EPI) sequence (TE 30 ms, flip angle 90°, TR 2000 ms, 116 kHz acquisition bandwidth) sensitive to blood oxygenation level-dependent (BOLD) contrast. In total, 1212 functional images were acquired in a single run. Prior to the functional imaging, 30 two-dimensional anatomical T1-weighted MDEFT images and 30 T1-weighted EPI images with the same spatial orientation as the functional data were acquired. The EPI acquisition was continuous to prevent periodic silent gaps between TRs to disrupt the participants' encoding of the rhythms. A slice acquisition frequency of 15 Hz was chosen to ensure the continuous scanner noise to be well above the fastest frequency of elements of the rhythmical stimuli (12.5 Hz) to prevent an auditory interaction between the two sources of rhythmic patterns and ensure that the participants were able to attend to the stimuli. By conducting an auditory test (56 sec) with the EPI sequence prior to data acquisition the sound level was adjusted for each participant in such a way that the stimuli could be easily heard over the scanner noise by each participant at an individually comfortable sound pressure level. When explicitly asked in a post experimental interview, participants reported no difficulty hearing the stimuli during the whole course of the measurement or performing any of the tasks.

6.2.4. Judgment analysis

For each individual participant, a linear mathematical model (individual case model) of judgment strategy was computed to examine the influence of stimulus properties on aesthetic judgments (Brehmer & Joyce, 1988; Cooksey, 1996; Jacobsen, 2004; Jacobsen et al., 2006). To this end, multiple regressions were computed using the stepwise method, including all properties of the 108 musical rhythms in the aesthetic judgment task as potential predictors of individual performance: tempo (slow = ”1”, middle = ”2”, fast = ”3”), measure (3 beats = ”1”, 4 beats =”2”, 5 beats = ”3”), subdivision (3 elements per beat = ”1”, 4 elements per beat = ”2”, 5 elements per beat = ”3”), rhythmic figure (long followed by short interval = ”1”, short followed by long interval = ”2”) and instrument type (”bongo” = ”1”, ”rock” = ”2”). The latter two, being nominal, were assigned ”dummy” variables. For example, a musical rhythm with a slow beat frequency, three beats per measure, four elements per beat, a long-short figure, consisting of predominantly metal drum sounds (”rock”) was assigned tempo = 1, measure = 1, subdivision = 2, rhythmic figure = 1 and instrument type = 2. In principle, the orthogonality of all stimulus properties as implemented in the experimental design allowed for all predictors to enter the model simultaneously. However, only variables providing incremental explanation of variance (p-value less than or equal to .05) entered the model. The beta weights of the predictors which did enter the individual model were taken to reflect the subject’s individual preferences (e.g., Cooksey (1996); Table 6.2). In an additional step of the analysis, the individual predictor beta weights were used to categorize the subjects for the subsequent BOLD-analysis (cf. Figure 6.2 2). In case the predictors tempo and instrument, which were the most important ones at the group level, did not enter an individual case model of a subject (p-value higher than .05), the enter method of multiple regression was used, which includes all specified predic-

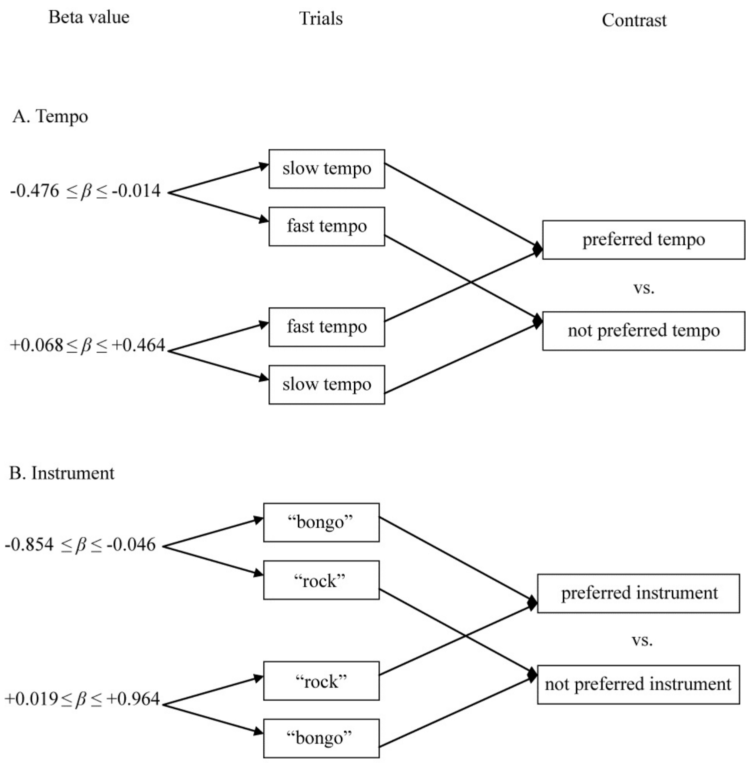


Figure 6.2.: *Grouping of trials for the BOLD-contrasts preferred vs. not preferred tempo and preferred vs. not preferred instrument. The grouping was performed according to Table 6.2, i.e., each subjects’ beta weights for tempo and instrument obtained by multiple regression (individual case models), which describe the influence of each stimulus property of the musical rhythm on individual aesthetic judgments. In subjects with negative weights for tempo, slow tempo trials were classified as preferred tempo and fast tempo were classified as not preferred tempo. In subjects with positive beta weights for tempo, fast tempo trials were classified as preferred tempo and slow tempo trials were classified as not preferred tempo. Consequently, for instance, slow tempo trials in subjects with a preference for slow tempo and fast tempo trials in subjects with a preference for fast tempo were grouped together under the condition ”preferred tempo”. The trial grouping according to instrument preference followed the same logic.*

tors in the model irrespective of the significance of their contribution. This way, full models were computed to obtain the respective beta weights, irrespective of their significance. These beta weights provided information on the mere tendency of every subject to prefer rhythms with slow tempo (negative beta weights) or fast tempo (positive beta weights), as well as the instrument type ”bongo” (negative beta weights) or ”rock” (positive beta weights). Note that this approach of classification according to beta weights is rather conservative, since the effect is not magnified by forming groups of subjects with extreme values.

6.2.5. MRI Data analysis

Functional data were motion-corrected online with the Siemens motion correction protocol (Siemens, Erlangen, Germany). Further processing of the fMRI data was performed using the software package LIPSIA (Lohmann et al., 2001). To correct for the temporal offset between the slices acquired in one image, a cubic-spline interpolation was employed. Low-frequency signal changes and baseline drifts were removed using a temporal highpass filter with a cutoff frequency of 1/96 Hz. Spatial smoothing was performed with a Gaussian filter of 5.65 mm FWHM. To align the functional data slices with a 3D stereotactic coordinate reference system, a rigid linear registration with six degrees of freedom (3 rotational, 3 translational) was performed. The rotational and translational parameters were acquired on the basis of the MDEFT (Norris, 2000) and EPI-T1 slices to achieve an optimal match between these slices and the individual 3D reference data set. This 3D reference data set was acquired for each subject during a previous scanning session. The MDEFT volume data set with 160 slices and 1mm slice thickness was standardized to the Talairach stereotactic space (Talairach & Tournoux, 1988). The rotational and translational parameters were subsequently transformed by linear scaling to a standard size. The resulting parameters were then used to transform the functional slices using trilinear interpolation, so that the resulting functional slices were aligned with the stereotactic coordinate system, thus generating output data with a spatial resolution of 3 x 3 x 3 mm (27 mm^3). The statistical evaluation was based on a least-squares estimation using the general linear model for serially autocorrelated observations (Friston, 1994; Friston et al., 1995a,b; Worsley & Friston, 1995). The design matrix was generated with a synthetic hemodynamic response function (Friston et al., 1998; Josephs et al., 1997) and its first derivative modeled at the onset of the stimuli and at trial onset in the resting condition. The model equation, including the observation data, the design matrix and the error term, was convolved with a Gaussian kernel of dispersion of 4 s FWHM to deal with the temporal autocorrelation (Worsley & Friston, 1995). In the following, contrast-images, i.e. beta value estimates of the raw-score differences between specified conditions, were generated for each participant. As noted before, each individual functional dataset was aligned with the standard stereotactic reference space, so that a group analysis based on the contrast-images could be performed. One-sample t-tests were employed for the group analyses across the contrast images of all subjects, which indicated whether observed differences between conditions were significantly distinct from zero. T values were subsequently transformed to Z scores.

To correct for false-positive results, in a first step, the initial voxelwise z-threshold was set to $Z = 2.576$ ($p = .005$, uncorrected) for the main contrast beautiful vs. not beautiful and the contrast tempo judgment (TJ) vs. resting condition (RC) used in a subsequent conjunction analysis, as well as $Z = 2.33$ ($p=.01$, uncorrected) for the contrast preferred vs. not preferred tempo and preferred vs. not preferred instrument. In a second step, the results were corrected for multiple comparisons using cluster-size and cluster-value thresholds obtained by Monte-Carlo simulations at a significance level of $p<.05$. In order to determine which of the areas enhanced during aesthetic judgment could be due to preference of tempo and which due to preference of instrument, the contrast preferred tempo vs. not preferred tempo and preferred instrument vs. not preferred instrument was masked by the contrast beautiful vs. not beautiful.

Additionally, the signal change in several functionally defined regions of interest (ROIs) was analyzed. A ROI was defined as the peak voxel of a premotor (a priori hypothesis), an anterior cingulate and cerebellar area (identified in a post-hoc analysis) that was activated relatively more for musical rhythms judged as beautiful in contrast to not beautiful or for rhythms with a preferred in contrast to a not preferred tempo masked by the contrast beautiful vs. not beautiful. Within each ROI, the percentage signal change was calculated in relation to the mean signal intensity across all time steps. Subsequently, the mean signal change over a four second epoch, starting five seconds after stimulus onset, was extracted for each condition and participant. Correlational analyses were performed using standard Pearson correlation coefficient and Pearson correlation significance (two-tailed) on percent signal changes to examine the functional association between activity in premotor and anterior cingulate ROIs. Cases with a Cook's distance index (Cook & Weisberg, 1980) above the value of one, a measure of how much the residuals of all cases would change if a particular case were excluded from the calculation of the regression coefficients, were considered as outliers. A repeated-measure analysis of variance (ANOVA) with the factors TASK (aesthetic judgment/tempo judgment) and PREFERENCE (preferred tempo/not preferred tempo) was computed for the percent signal change in the premotor ROI identified by the contrast preferred versus not preferred tempo during aesthetic judgment masked by the contrast beautiful vs. not beautiful.

The anatomical locations of the functional activation were assigned by considering both the peak voxel and the position of the respective activation cluster in

Talairach stereotaxic space (Talairach & Tournoux, 1988) for cortical and subcortical activations. The MRI atlas of the cerebellum by Schmahmann et al. (2000) was used to locate cerebellar activations. For this purpose, Talairach coordinates of cerebellar activation were converted to MNI305 space by an algorithm implemented in the GingerALE application (Laird et al., 2005; Lancaster et al., 2007).

6.3. Results

6.3.1. Behavioral results

Behavioral performance was assessed by error rates in the control condition (CC), reaction times and frequency of response. 94.0% (1.7 SE) of all responses in the CC were correct. There were 0.1% non-responses and 5.9% erroneous responses. Aesthetic judgment (AJ) responses showed 0.5% non-responses and tempo judgment (TJ) 0.1% non-responses. 47.2% (3.3 SE) of the stimuli under the aesthetic judgment task were judged as beautiful, 52.8% as not beautiful, the difference being not significant (p=.409, paired t-test). 51.9% (2.4 SE) of the stimuli under the tempo judgment condition were judged as fast, 48.5% (2.4 SE) as not fast, the difference being not significant (p=.485, paired t-test). 90.1% (1.7 SE) of the musical rhythms with a fast beat frequency (tempo) were judged as fast, 81.6% (2.4 SE) of the musical rhythms with a slow tempo were judged as not fast. Mean response times and standard errors (in parentheses) were as follows: beautiful (aesthetic judgment ”yes”) 2042 ms (123 ms); and not beautiful (aesthetic judgment ”no”) 2036 ms (121 ms); fast (tempo judgment ”yes”) 1564 ms (127 ms); and slow (tempo judgment ”no”) 1710 ms (118 ms). A repeated-measures ANOVA over the judgment latencies with the factors TASK (AJ/TJ) and ANSWER (yes/no) revealed a main effect of TASK (F(1,17) = 4.61, p<.05) and an interaction (F(1,17) = 4.61, p<.05).

Further investigation of the interaction TASK by ANSWER showed an effect of judgment latencies for ANSWER under the tempo task ($p<.03$, Bonferroni corrected), with delayed response for stimuli that were judged as slow. One additional subject (see methods/participants) had to be excluded from analysis due to the fact that he judged all stimuli as beautiful in the aesthetic judgment condition, although all participants were instructed to judge each rhythm in relation to previous rhythms in the experiment.

For 15 out of 18 participants, a substantial individual case model was derived. Standardized regression coefficients (beta weights) and multiple regression coefficients (R) are shown in Table 6.1. The remaining three participants did not show a significant linear relationship between any of the stimulus properties and their judgments.

Instrument type was found to be the most important stimulus property determining participants' aesthetic judgments (cf. Table 6.1).

As predicted by pilot testing, tempo was the most influential time-related stimulus property determining participants' aesthetic judgments at the group level with beta weights ranging from -0.48 to 0.46. However, for half of the participants tempo was not a significant predictor for aesthetic judgments. To determine whether these subjects tended to prefer slow or fast tempo, even though the preference was not pronounced, the beta weights we obtained for the remaining subjects using the enter method of multiple regression which includes all specified predictors in the model irrespective of the significance of their contribution to the model (cf. Table 6.2). To allow a subsequent analysis of the BOLD response to preference for the most important time-related predictor - tempo, the participants were divided into two groups on the basis of the beta weights for tempo, of which one group tended to prefer fast (positive beta weights) and the other group slow tempo (negative beta

Table 6.1.: *Individual linear mathematical models (individual case models) of judgment strategy computed to examine the influence of stimulus properties on aesthetic judgments. Standardized regression coefficients and multiple regression coefficients (R) as obtained by stepwise multiple regression are shown. Columns show all predictors of preference judgments (tempo, measure, beat subdivision, rhythmic figure and instrument type; the latter two, being nominal, were assigned dummy variables.). Each subjects most important predictor for the judgment beautiful is in bold font.*

subject	**tempo**	**measure**	**subdivision**	**rhythm. fig.**	**instrument**	**R**
1	**0.271**				-0.259	0.373
2					**-0.796**	0.796
3					**-0.248**	0.248
4						/
5					**-0.443**	0.443
6						/
7	-0.229		-0.229		**-0.460**	0.563
8	**-0.414**					0.414
9	**-0.476**		-0.251		0.389	0.664
10	**0.464**				0.178	0.497
11	-0.204		-0.181		**0.500**	0.570
12						/
13					**-0.778**	0.778
14	0.227		0.204		**-0.482**	0.565
15					**-0.854**	0.854
16					**0.964**	0.964
17	0.253		**-0.282**			0.379
18	**-0.277**		-0.231			0.361

weights). Two out of 18 subjects had to be excluded from classification having beta weights of zero, and thus indicating the absence of a linear preference trend towards slow or fast tempo. Thus 16 subjects could be classified with regard to their tendency to prefer slow (eight subjects) or fast tempo (eight subjects), so that attention both to preferred and not preferred tempo during the aesthetic task contained an equal amount of slow and fast tempo trials on the single-subject and the group level, respectively (cf. Table 6.2 and Fig. 6.2).

The individual beta weights for tempo ranged from -0.01 to -0.48 in the group that preferred slow and from +0.07 to +0.46 in the group that preferred fast tempo. The same procedure was employed for instrumental preference (cf. Fig. 6.2). All subjects could be classified with regard to their tendency to prefer ”bongo” (10 subjects) or ”rock” (eight subjects), so that attention both to preferred and not preferred instrument contained an equal number of trials with the instrument types ”bongo” and ”rock” on single-subject and approximately the same on group level, respectively. Here the individual beta weights for instrument type ranged from -0.046 to -0.854 in the group that preferred ”bongo” and from +0.019 to 0.964 in the group that preferred ”rock”.

Furthermore, participants for whom a substantial individual case model was obtained revealed differences in linear predictability, i.e., the degree to which individual judgments captured using a linear equation differed between participants. Multiple R’s ranged from 0.25 to 0.96, i.e., a range of explained judgmental variance from 6% to 92%Ḋifferences in explained variance are typically interpreted as an index of strategy use (Steward, 1988). Participants with a higher linear predictability, i.e., stronger linear relationships, used systematic judgment strategies, while linearly unpredictable judges most likely employed highly configural cue combinations, i.e., particular configurations of combinations of stimulus features (Brehmer & Joyce, 1988; Cooksey, 1996).

Table 6.2.: *Grouping of subjects according to tempo and instrument preference. Standardized regression coefficients (beta weights) for tempo (A.) and instrument type (B.), which describe the influence of these predictors on individual aesthetic judgments, were obtained by stepwise (*) and enter multiple regression. Due to the linear mathematical modeling, these beta weights provided information on the tendency of every subject to prefer rhythms with slow tempo (negative beta weights) or fast tempo (positive beta weights), as well as the instrument type bongo (negative beta weights) or rock (positive beta weights). Subjects are sorted according to the respective absolute value of beta weights for tempo and instrument separately. They were divided according to their tendency to prefer slow (negative beta weights) and fast (positive beta weights) (A.), as well as instrument type A (negative beta weights) and B (positive beta weights) (B.), respectively. This information was used to determine differences in BOLD-response during trials with preferred compared to not preferred tempo and preferred compared to not preferred instrument type (cf. Fig. 6.2 for the grouping of trials according to preference).*

A.			**B.**		
subject	**preferred tempo**	**tempo (beta weight)**	**subject**	**preferred instrument**	**instrument (beta weight)**
1	slow tempo	-0.476*	12	bongo	-0.854*
2		-0.414*	9		-0.796*
3		-0.277*	11		-0.778*
4		-0.229*	15		-0.482*
5		-0.204*	4		-0.460*
6		-0.127	7		-0.443*
7		-0.024	17		-0.259*
8		-0.014	6		-0.248*
9		0	8		-0.130
10		0	16		-0.046
11	fast tempo	0.068	13	rock	0.019
12		0.091	14		0.094
13		0.094	2		0.131
14		0.184	3		0.151
15		0.227*	18		0.178*
16		0.253*	1		0.389*
17		0.271*	5		0.500*
18		0.464*	10		0.964*

Finally, since tempo was an important cue for the aesthetic judgment, it was crucial to rule out on the behavioral level that the aesthetic judgment can be explained by explicit tempo judgments (i.e., ”fast, therefore beautiful” or ”fast, therefore not beautiful” depending on the preferences, respectively). A one-tailed correlation between the beta weights for preferred tempo, which indicated how much there was a tendency to prefer fast (positive value) or slow tempo (negative value), and the percentage of accurate classification of fast and slow tempo, respectively, did not reveal any significant relationship (beta weight for preferred tempo and correct classification of fast tempo: r=-.300; p=.113; beta weight for preferred tempo and correct classification of slow tempo: r=.136; p=.295).

6.3.2. fMRI results

Beautiful vs. not beautiful judgments

As hypothesized, trials presenting rhythmic stimuli that were judged as beautiful led to significantly stronger bilateral activations within inferior ventral premotor cortex, which extended into the frontal opercular cortex adjacent to the anterior insula, the so-called precentral operculum (PCO/PMv; Brodmann Area (BA) 6; Peters & Jones (1985)), and in the cerebellum (superior semilunar lobule bilaterally, left lobule simplex and left inferior semilunar lobule) (cf. Fig. 6.3A and Table 6.3). Additionally, activations were found in the anterior cingulate cortex (ACC; BA 24), the right superior frontal gyrus (BA 10) and the middle frontal gyrus (BA 9).

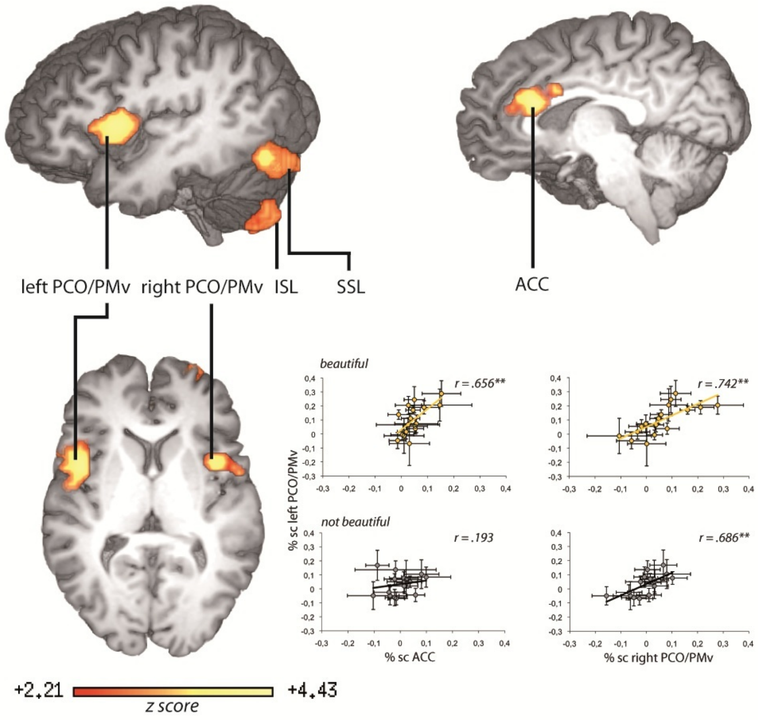
Importantly, the above activity pattern was preserved when excluding six subjects who received instrumental training or attended a choir at some point in their life in addition to the regular musical education at school, indicating that these results were not driven by musical education (cf. Fig. A.1).

In a subsequent post-hoc analysis was perfomed to identify whether there was

Table 6.3.: *Activation foci in Experiment 1: Anatomical specification, hemisphere (R right, L left), Talairach coordinates (x, y, z) and maximal Z scores (Z) of significant activations in the direct contrasts. ACC: anterior cingulate cortex; aMFG: antero-medial frontal gyrus; BA: Brodmann area; MFG: middle frontal gyrus; PCO: precentral operculum; PMv: ventral premotor cortex; SFG: superior frontal gyrus; Z = z-score.*

Brain region	**Hemisphere**	**x**	**y**	**z**	**Z**
Beautiful vs. Not Beautiful Rhythms					
PCO/PMv (BA 6)	L	-41	4	9	3.82
PCO/PMv (BA 6)	R	37	7	12	3.53
Crus I	L	-29	-80	-12	4.61
Crus I	R	40	-62	-12	3.65
Lobule VI	L	-23	-65	-21	3.63
Crus II	L	-35	-74	-42	3.61
ACC (BA 24)	R	4	19	21	4.38
SFG (BA 10)	R	22	58	0	3.83
MFG (BA 9)	R	22	37	21	3.54
Preferred Tempo vs. Not Preferred Tempo (AJ)					
PMv (BA 6)	L	-53	1	24	3.82
Putamen	R	28	-17	12	3.67
Thalamus. pulvinar	R	7	-26	12	3.39
Aesthetic Judgment (AJ) vs. Tempo Judgment (TJ)					
aMFG (BA 9)	L	-5	55	27	3.55
aMFG (BA 9/32)	R	-2	43	21	3.51
aMFG (BA 10)	R	13	52	9	3.36
Anterior ventral insula	L	-32	16	-3	4.19
IFG		-32	31	-12	3.64
Midbrain	L	-14	-23	-12	3.42
Pons	R	-2	-32	-21	3.6

A *beautiful vs. not beautiful rhythms*



B *preferred vs. not preferred tempo (AJ)*

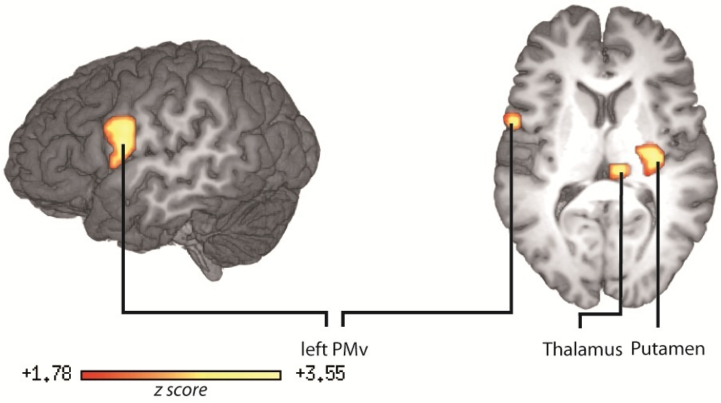


Figure 6.3.: *Effects of rhythmical preference. A. Areas elevated for rhythms judged as beautiful compared to not beautiful (beautiful vs. not beautiful rhythms). Scatter diagrams indicate correlations of percentage signal changes in left PCO/PMv and ACC, as well as left and right PCO/PMv during beautiful and not beautiful judgments, respectively. Each data point represents the mean and standard error of the percent signal change for each subject and location. B. Areas elevated for preferred tempo vs. not preferred tempo. The overlap between the contrast beautiful vs. not beautiful and preferred tempo vs. not preferred tempo during the aesthetic judgment task revealed a significant activation in the left PCO/PMv (-50 4 12, Z = 2.72; 54 mm3).*

a response-specific linear relationship between ACC and PCO/PMv, areas that are known to be related to voluntary initiation/suppression of emotional vocal utterances and control of learned vocal patterns, respectively (Jurgens, 2002, 2008; Jurgens & von Cramon, 1982). To express quantitatively the relationship in activation of these regions as a function of preference, the percentage signal change was extracted from the peak voxel in the respective ROIs that were defined by the contrast beautiful vs. not beautiful in each subject. Pearson correlation coefficients were computed for ACC and left PCO/PMv, ACC and right PCO/PMv, as well as left and right PCO/PMv. ACC and left PCO/PMv correlated in trials judged as beautiful (r=0.656**, p<.005), but not in trials judged as not beautiful (r=0.193, p=.458), after excluding an outlier (with outlier: r=0.578*, p<.05 and r=0.253, p=.311). There was no correlation in either aesthetic judgment between ACC and the right PCO/PMv (Beautiful: r=0.382, p=.131; Not Beautiful: r=0.373, p=.141), whereas a significant correlation between right and left PCO/PMv was preserved during both aesthetic judgments (Beautiful: r=0.742**, p<.005; Not Beautiful: r=0.686**, p<.005), pointing to a functionally invariant relationship. The percent signal changes between ventral premotor and cerebellar sites (superior semilunar lobule bilaterally) did not yield any significant correlations in beautiful or in not beautiful judgments.

Preferred tempo vs. not preferred tempo

In addition to a general effect of preference for musical rhythms, it was examined which of the above components could be traced back to the preference for the most important time-related property determining whether a musical rhythm was judged as beautiful or not. In accordance with previous studies that demonstrated the importance of tempo in auditory rhythms perception (Baruch & Drake, 1997; Bella et al., 2001; Drake et al., 2000; Trainor et al., 2004) and sensorimotor coupling (Chen et al., 2006; Drake et al., 2000; Fraisse, 1982; Large, 2000; Moe-

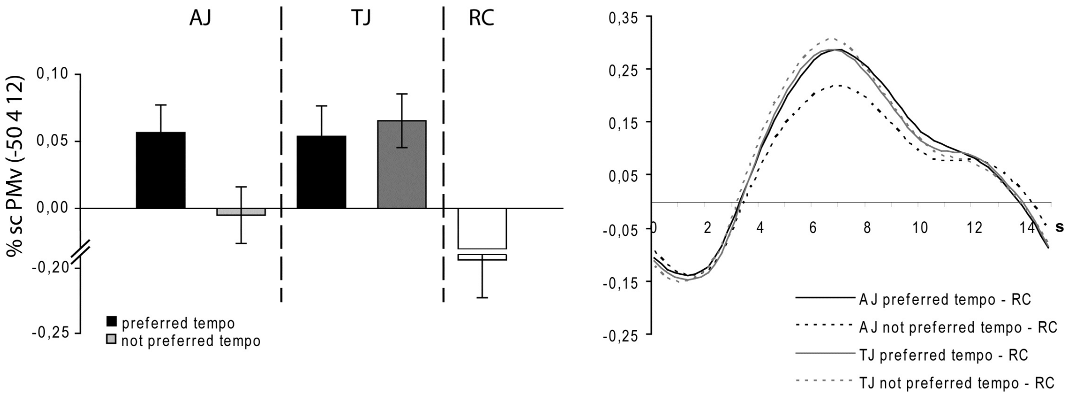


Figure 6.4.: *Effects of tempo preference on premotor activity. Percent signal change (% sc) for musical rhythms with preferred and not preferred tempo during the aesthetic (AJ) and tempo judgment (TJ) conditions, as well as % sc during the resting condition (RC) in the ventral premotor ROI (-50 4 12; identified by the overlap between the contrast preferred vs. not preferred tempo during the aesthetic judgment task and the contrast beautiful vs. not beautiful). In the timeline chart, the onset corresponds to the onset of the respective stimulus and the % sc during the AJ and TJ conditions is depicted relative to the % sc of the RC.*

lants, 2002, 2003; van Noorden & Moelants, 1999), tempo was the most influential time-related property both in preceding pilot testing and in the behavioral results of the fMRI experiment (Table 6.2). The preference for slow or fast tempo was identified in every subject by judgment analysis (cf. Methods/Judgment analysis and Results/Behavioral results for classification procedure). The contrast between attention to preferred vs. not preferred tempo during the aesthetic judgment task masked by the contrast beautiful vs. not beautiful yielded a significant activation in the left PCO/PMv only (-50 4 12; Z = 2.72; 54 mm3). There was an interaction between TASK (aesthetic judgment/tempo judgment) and PREFERENCE (preferred tempo/not preferred tempo) in the above premotor ROI (repeated measures ANOVA; F(1,15) = 5.018; p<.05) with a pronounced percent signal change difference between preferred and not preferred tempo only during the aesthetic, but not the tempo judgment task (Fig. 6.4).

In line with this finding, a conjunction analysis revealed a common activation of the left PMv (-53 2 15; Z = 3.72; 1026 mm^3) both during the tempo task vs. rest and preferred vs. not preferred tempo in the aesthetic judgment task.

Besides the ventral premotor overlap between the contrasts preferred vs. not preferred tempo during the aesthetic judgment task and beautiful vs. not beautiful, musical rhythms with preferred tempo during the aesthetic judgment task elevated activity in the lateral and superior part of the left ventral premotor cortex (PMv; BA 6), as well as the putamen and the pulvinar nucleus of the thalamus (Fig. 6.3 and Table 6.3).

As in the valence analysis (beautiful vs. not beautiful judgments), the above activity pattern was preserved when excluding five subjects who received instrumental training or attended a choir at some point in their life in addition to the regular musical education at school (Fig. A.1). Moreover, individual percent signal change data revealed that in the PMv, the hemodynamic signal increase when listening to musical rhythms with a preferred tempo was not driven by musical training (r=-.08; p=0.384; one-tailed), but rather by how strongly a subject preferred a tempo (r =.626; $p<0.01$; one-tailed), as expected from the categorization of preferred and not preferred tempo (Fig. A.2).

Preferred instrument vs. not preferred instrument

To determine whether the activation of the left PCO/PMv was related to tempo preference and not to instrumental preference, it was evaluated whether instrumental preference was accompanied by activity in this area. The preference for instrument type was identified in every subject by judgment analysis (cf. Methods/Judgment analysis and Results/Behavioral results for classification procedure). The contrast between attention to preferred vs. not preferred instrument during the aesthetic judgment task masked by the contrast beautiful vs. not beautiful did not yield significant activation in the left PCO/PMv, but extended cerebellar activations, partic-

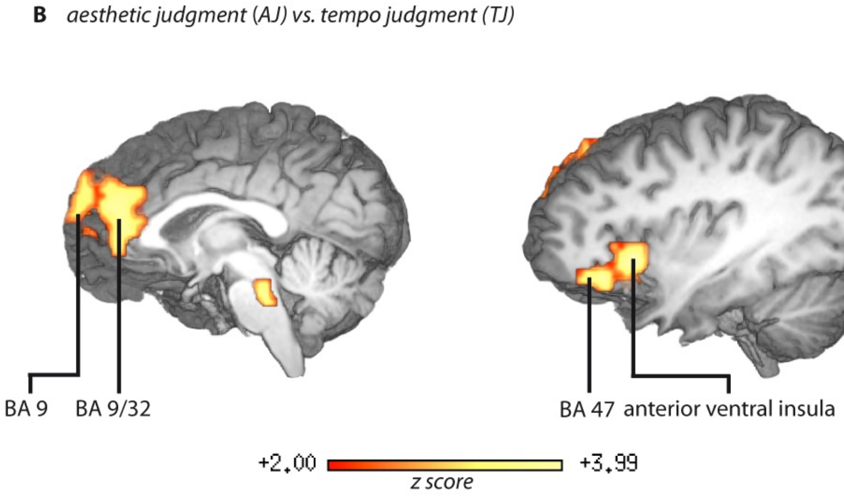


Figure 6.5.: *Significantly activated areas for aesthetic as opposed to tempo judgments.*

ularly in the superior semilunar lobule bilaterally (-32 -77 -9; Z = 2.95; 594 mm3; and 28 -71 -12; Z = 3.48; 1782 mm3).

Aesthetic judgment vs. tempo judgment

As tempo was the most important time-related cue for aesthetic judgments, one might argue that aesthetic judgments of rhythms simply amount to explicit tempo judgments (i.e., ”slow, therefore beautiful” or ”slow, therefore not beautiful”, respectively), which would mean that subjects bypassed the instruction to deliver an evaluative judgment. Therefore, a direct contrast between preference and tempo judgment tasks was computed. Significant cortical activity differences were observed in the anterior ventral insula, the antero-medial frontal gyrus (BA 9, BA 9/32, and BA 10) and the inferior frontal gyrus (BA 47) (Fig. 6.5 and Table 6.3). There was no significant activation for the reverse contrast (tempo vs. aesthetic judgment).

6.4. Discussion

In *Experiment 1* fMRI was conducted to investigate how aesthetic appreciation of musical rhythms modulates activity in motor-related areas. As expected, the results demonstrate that attention to preferred musical rhythms correlated with activity increase in a network of motor-related areas. In particular, musical rhythms judged as beautiful compared to not beautiful enhanced the BOLD response bilaterally in the precentral operculum/ventral premotor cortex (PCO/PMv; BA 6) and in the cerebellum.

Moreover, the results show that preference-associated effects in the motor areas induced by musical stimuli (Blood & Zatorre, 2001; Koelsch et al., 2006) emerge even when musical appraisal is reduced to that of tempo (beat frequency) alone, i.e. to a time-related feature that provides a pulse people tune in to when listening to music (Chen et al., 2006; Drake et al., 2000; Fraisse, 1982; Large, 2000; Moelants, 2002, 2003; van Noorden & Moelants, 1999). Activity in the PMv increased not only during attention to musical rhythms judged as beautiful, but, more specifically, also during attention to rhythms with a preferred tempo. These findings extend research on auditory and visual timing, showing that the motor system is not only engaged during attention to rhythm in general (Bengtsson et al., 2009; Chen et al., 2008; Coull et al., 2004; Grahn & Brett, 2007; Schubotz et al., 2000, 2003; Wolfensteller et al., 2007), but more specifically, that it is more engaged for preferred rhythm.

Since subjects were asked to deliver an aesthetic (or, more generally, an evaluative) judgment, it was important to examine in more detail how they behaved under this instruction. To this end, two controls were employed: Firstly, we sought to rule out that aesthetic judgments of rhythms simply amount to explicit tempo judgments. In that case, subjects would have bypassed the instruction to deliver an evaluative judgment. However, the absence of significant correlations between tempo preference and performance on the tempo judgment task is in line with the assumption of independent behavioral mechanisms underlying these tasks. Importantly, the significant hemodynamic differences between aesthetic appraisal of rhythm and temporal judgments demonstrated that the subjects engaged in an evaluative in contrast to a tempo identification task: The antero-medial and inferior frontal activations directly replicated the findings of a study on aesthetic judgments of abstract visual patterns (Jacobsen et al., 2006). Secondly, a judgment analysis allowed us to examine the strategies underlying these evaluative judgments. The systematic influence of the different constituents of the musical rhythms on the subjects' aesthetic judgments was probed on the basis of individual case models (Brehmer & Joyce, 1988; Cooksey, 1996; Jacobsen, 2004; Jacobsen et al., 2006) and determined each subject's preferences for the two most influential constituents ruling individual aesthetic judgments of the musical rhythms - instrument type (either ”bongo” or ”rock”) and tempo (either fast or slow). This enabled us to dissociate the influence of tempo and instrumental preference on activity enhancement in motor-related areas elevated by rhythms judged as beautiful. Hence, the network identified for beautiful as compared to not beautiful rhythms could be decomposed, revealing one component related to tempo preference (PCO/PMv) and the other related to instrumental preference (cerebellum).

The PMv activated during preferred rhythms and tempo and its adjacent areas, the inferior frontal gyrus and the Rolandic operculum, have been shown to be involved in voice-related tasks, such as singing (Ozdemir et al., 2006; Perry et al., 1999) and speech (Wildgruber et al., 1996), as well as singing imagery (Kleber et al., 2007; Riecker et al., 2000) and speech imagery (Rauschecker et al., 2007; Shergill et al., 2006). The premotor activation most likely overlaps with the precentral area crucial for the control of learned vocal patterns, e.g. in speech and song. When this region is electrically stimulated, movements of the vocal chords are triggered in human and non-human primates (Jurgens, 2002; Penfield & Rasmussen, 1952). Furthermore, if it is damaged bilaterally in humans, singing and speaking is no longer possible (Groswasser et al., 1988). In squirrel monkeys, it has been shown to be a part of the motorcortical pathway, which controls the patterning of learned vocal utterances via the reticular formation (Jurgens, 2008). The activation of a vocalization-related premotor area supports our hypothesis based on the notion of a correspondence of movement execution or imagery and attention to external events in the premotor cortex (Schubotz et al., 2003; Wolfensteller et al., 2007). Following the account of the ”Habitual Pragmatic Event Map” (Schubotz, 2007), which proposes a generic framework for the neural overlap of motor and non-motor cognitive functions, activity in the premotor cortex is structured according to the modes of transformations such as rotation, deformation, or acceleration, which self-induced as well as observed events can undergo. More specifically, the inferior ventral premotor region has been associated with attention to event change affected by ac-/deceleration (Schubotz & von Cramon, 2001b; Schubotz et al., 2003; Thaut, 2003; Wolfensteller et al., 2007) and pitch rising/falling (Brown & Martinez, 2007; Meyer et al., 2004; Schubotz & von Cramon, 2002b). These changes are at the heart of both vocalization and articulation. Similarly, external temporal events such as musical rhythms and especially the tempo of a musical rhythm involve changes defined by ac-/deceleration. Thus, as established for the domain of action performance, imagery, and observation, motor networks may be considered providing forward models that enable attention to change beyond the action domain (Grush, 2004; Wolpert & Flanagan, 2001).

Notably, studies have reported the enhancement of dorsal instead of ventral premotor cortex activity during timing tasks (Chen et al., 2006; Lewis et al., 2004). However, this discrepancy may be due to differences between experimental paradigms such as the use of finger tapping in the above mentioned studies. A systematic comparison between motor and non-motor timing paradigms would be valuable in order to clarify the functional contributions of the network components (Schubotz & von Cramon, 2001a).

How can the boosting effect of rhythmic preference on premotor activity be explained? The comparison of tempo preference effects on PMv activity during the aesthetic and tempo judgment tasks, as well as the premotor activity increase common to both preferred tempo and the tempo judgment task shed light on the cognitive and neural mechanisms underlying this effect. According to the framework of sensorimotor forward models (Grush, 2004; Schubotz, 2007; Wolpert & Flanagan, 2001), to accomplish a perceptual rhythm task such as the tempo task, i.e. to judge whether a musical rhythm is fast or not, the subjects had to map the incoming external beat frequency of the musical rhythms on their audiomotor representation of a template established on the basis of previous rhythms, no matter whether it was preferred or not. The effect of preferred tempo on the percent signal change in the PMv during the aesthetic judgment task and the tempo judgment control (cf. Fig. 6.4) provides physiological evidence that attention to preferred tempo recruited neural recourses in the premotor cortex which have been shown to support perceptual rhythm tasks: The data pattern shows that activity during the aesthetic judgment task increased to the level of the tempo judgment task only when subjects were listening to the tempo they preferred. Accordingly, a conjunction analysis revealed that both during preferred (compared to not preferred) tempo and during the tempo judgment task (compared to rest) activity increases in the PMv. These analyses thereby corroborate the assumption that ventral premotor activity during preferred tempo is driven by enhanced sensorimotor simulation of the external beat frequency of the musical rhythms, i.e. by computations also recruited during the tempo task.

Interestingly in this context, the lateral premotor cortex is discussed to compensate the functional impairment of the basal ganglia-SMA loop during voluntary movement in Parkinson's disease (PD) in the presence of external visual as well as auditory pacing cues (Hanakawa et al., 1999; McIntosh et al., 1997; Okuma, 2006). In line with these findings, a study contrasting listening to tones occurring at equal time intervals, thus constituting an external beat, and not equal time intervals has demonstrated an enhanced activity in the pars opercularis of the inferior frontal gyrus, which is adjacent to the PMv (Bengtsson et al., 2009). All musical rhythms in *Experiment 1* provided such an external isochronous cue due to the continuous presence of an overt beat. This is different from studies in which the underlying beat has to be inferred from the auditory rhythmic structure (beat induction) - a process that is suggested to be subserved by the SMA and the putamen and that is impaired in PD patients (Chen et al., 2008; Grahn & Brett, 2007). Since the PMv has been shown to enable expectations of incoming auditory rhythms(Schubotz et al., 2004), the enhanced activity in the PMv during preferred tempo may support accurate synchronization to an external beat and facilitate the tuning-in to the beat of music that people prefer. Thus, our findings point to a possible significance of preference in sensorimotor coupling during auditory rhythms. Future studies should assess, whether the presence of a preferred beat frequency can increase the therapeutic effect of synchronisation to an external beat on gait and speech reported in PD patients (Baker et al., 2008; McIntosh et al., 1997; Thaut et al., 1999, 2001; van Wegen et al., 2006; Willems et al., 2007).

Can the effects reported in *Experiment 1* be distinguished from motor imagery of a tuning-in behavior such as head nodding, toe tapping or humming? Our findings confirm this interpretation: Firstly, the co-activation of the PCO/PMv signal elevated for rhythms judged as beautiful with a peri-genual aspect of the ACC (BA 24), which was not predicted initially, may point to a suppression of overt tuning-in to an external rhythm during preferred rhythms, but not to a motor imagery of an internally generated rhythm. A post-hoc ROI analysis revealed that while the signal change between the left and right PCO/PMv significantly correlated both during ”beautiful” and ”not beautiful” judgments, indicating an, in this respect, functionally invariant connection, the signal change in ACC and the PCO/PMv significantly correlated only during musical rhythms judged as beautiful, but not during those judged as not beautiful. The ACC has been shown to control the readiness to phonate, i.e. the voluntary initiation and suppression of vocal utterances via the periaqueductal grey and the reticular formation (Jurgens, 2008; Jurgens & von Cramon, 1982; Paus, 2001). In the reticular formation, the limbic pathway converges with the motorcortical pathway, and the output projects to phonatory motoneurons (Jurgens, 2008). Thus, it is conceivable that the reticular formation allows the ACC to inhibit the initiation of learned vocal patterns triggered by the PCO/PMv. That is to say, the more we prefer a musical rhythm, the lower is the motor threshold due to an increase in PCO/PMv activity, and the more inhibition is provided by the ACC to suppress overt vocalization. In *Experiment 1*, the enhanced ventral premotor activity during preferred musical rhythms may facilitate the sensorimotor transformation of the acoustic afference (rhythmic stimuli) to vocal and articulatory representations, whereas ACC performs a vocal gating function. Secondly, a motor imagery explanation cannot be reconciled with the absence of activation in dorsal premotor regions for neck and foot movements. And thirdly, there was no activity increase in areas characteristic for motor imagery and motor preparation such as the primary motor cortex, primary and secondary somatosensory areas, and especially the SMA/pre-SMA, an area which has been shown to be most reliably involved in vocal imagery (Kawashima et al., 2000; Kleber et al., 2007; Rauschecker et al., 2007; Riecker et al., 2000; Thobois et al., 2000). Thus, it seems more consistent with the data to consider premotor involvement during preferred rhythms and tempo as an audiomotor fraction of vocal and articulatory representations that are exploited during attention to external rhythmic events. Such a fraction misses proprioceptive-motor and other sensorimotor representations which are part of motor imagery, as well as movement.

Although such an audiomotor fraction exploits a circuit that is mainly involved in vocalization, this activity boost may facilitate effector-independent tuning-in behaviour including toe tapping or head nodding. It was found that the localization of attention-related activation in PM varies not as a function of the motor effector previously assigned to the attended stimulus, but rather of the produced effects (Wolfensteller et al., 2004). That means, with respect to PMv involvement here, it should make no difference whether a rhythm is produced by finger tapping, head nodding, foot tapping, or humming. Accordingly, Bengtsson et al. (2005) report activity enhancement in the left ventral BA6/BA44 both during rhythmic speech and during rhythmic left and right finger movement. Macaque studies have shown that there is a family of premotor neurons that is not tuned to motor effectors, but to the perceivable effect that a movement brings about. Thus, some grasping neurons are unspecific for limb and grip type, i.e., grasping a target with the right or left hand or the mouth can engage the same neuron (Rizzolatti et al., 1987). That is, of course, not to say that other premotor neurons are not tuned to motor effectors. Activity in PMv in *Experiment 1* may reflect a facilitation of producing preferred rhythms with an arbitrary motor effector, including fingers (Chen et al., 2008; Lahav et al., 2007; Zatorre et al., 2007).

Finally, attention to preferred tempo elicited higher activity in the right putamen. Apart from its recognized general function in timing mechanisms (Coull et al., 2008, 2004; Ferrandez et al., 2003; Nenadic et al., 2003; Rao et al., 1997, 2001), putamen activation is enhanced by the presence of a regular compared to an irregular beat. This has been shown both during an auditory rhythm discrimination task (Grahn & Brett, 2007) and during bipedal dance movements to music (Brown et al., 2006). In music the predominance of, and thus a preference for, a regular beat or repetitive temporal patterns is a cross-cultural universal, presumably because musical rhythms have their origin in the motor rhythms controlling locomotion, breathing and heart rate (Trainor, 2008). Since all the musical rhythms in this experiment had a regular beat, our results suggest that putamen activation can be modulated not only by beat regularity, but also by the preference for a beat frequency (tempo).

Using fMRI the issue of causality cannot be resolved, i.e. whether activation of the PMv is a function of the extent of the preference for a rhythm that we listen to or whether preference emerges as a function of the extent to which rhythms cause activity in the PMv. This should be addressed by future transcranial magnetic stimulation studies. If rhythmical preference is driven by PMv activity, rhythmical preferences should break down or vanish by inhibitory PMv stimulation; if, however, PMv activity is just an effect of rhythmical preference, rhythmical preferences should be preserved even in the presence of inhibitory PMv stimulation.

Experiment 1 demonstrates that the aesthetic appreciation of musical rhythms is accompanied by activity increase in parts of the motor system and thus lend support to the assumption that the motor-system-based internal simulation of rhythms can be enhanced by preference. Our findings point to a link between activity increase in the ventral premotor cortex during rhythms with a preferred tempo (beat frequency) and the tuning-in to the beat of music that we enjoy.

7. Experiment 2. H3-H4. Causal contribution of the PMv to auditory rhythmic preference (rTMS)

7.1. Introduction

A tight link exists between the motor system and preferred auditory rhythm (Todd et al., 1999). The tempo range of different popular musical styles has been shown to closely match that of repetitive movements such as locomotion (Moelants, 2003; van Noorden & Moelants, 1999). A series of behavioral studies demonstrated prior repetitive movement to prime preferences for musical rhythm in children and adults (Phillips-Silver & Trainor, 2005, 2007, 2008). Likewise, a strong association has been shown between spontaneous motor tempo and preferred tempo of auditory stimuli, which varies across age (McAuley et al., 2006) and between individuals (Todd et al., 2007). Accordingly, beat rate (tempo), a periodic auditory pulse with an inter-onset-interval in a sub-seconds range peaking around 2 Hz (van Noorden & Moelants, 1999) corresponds to the preferred frequency of repetitive movements in adult individuals (McAuley et al., 2006). A beat serves as a central auditory cue when synchronizing body movements to music (Drake et al., 2000; Fraisse, 1982; Kirschner & Tomasello, 2009; Styns et al., 2007) and appears to be a human universal (Nettl, 2000).

Despite the evidence for a coupling between preferred auditory tempo and movement, it is not fully understood how the central nervous system drives the preference strength for auditory beat rates, i.e. whether activity in motor-related regions contributes to this preference. Neuroimaging studies have provided evidence that subjectively pleasurable music is accompanied by activity increase in medial and lateral motor-related cortical regions - the supplementary motor area (SMA) and the Rolandic operculum, as well as the cerebellum (Blood & Zatorre, 2001; Koelsch et al., 2006), but these studies did not directly examine the link between these regional activity increases and the preference for specific rhythmic components, such as preferred auditory rhythm or beat rate. In order to investigate whether preferred tempo, a component considered to be most elementary with respect to coupling sound to movement (Cross, 2001; Janata & Grafton, 2003), leads to an activity increase in motor-related sites, *Experiment 1* was conducted, which involved rhythmic musical patterns (Kornysheva et al., 2010). On the basis of the subjects' individual aesthetic judgments, the analysis of the BOLD-response revealed an activity boost in premotor and cerebellar areas during the subjective appreciation of musical rhythms. Specifically, left ventral premotor (PMv) activity was enhanced for stimuli with a preferred tempo, but not for stimuli with preferred timbre (control variable). Furthermore, there was a significant correlation between the subjects' tendency to prefer a tempo (be it slow or fast) and the signal increase in the left PMv (Fig. A.2). While these results demonstrated that an activity increase in the left PMv very systematically accompanies musical rhythms with a preferred tempo, they did not allow to draw conclusions with regard to the contribution of the left

PMv to tempo preference. Is the left PMv co-activated with critical areas, but is itself not critical for tempo preference? Due to the observational nature of fMRI, it remains an open question whether activity in the left PMv directly contributes to tempo preference strength.

To directly address the contribution of left PMv activity on the strength of tempo preference, an offline repetitive transcranial magnetic stimulation (rTMS) study (*Experiment 2*) was conducted. Low-frequency repetitive TMS is a noninvasive method which is applied in order to temporarily disrupt activity in a restricted cortical area by a transient reduction of cortical excitability (Boroojerdi et al., 2000; Chen et al., 1997; Gerschlager et al., 2001; Maeda et al., 2000). It can provide insight into the causal role of a cortical area in behavior (Pascual-Leone et al., 2000), by showing that an interference with activity in this area can systematically affect behaviour. Given that the signal increase in the left PMv correlated with the subjects' tendency to prefer a tempo (Fig. A.2), it was hypothesized that PMv activity increase is not only associated with, but also affecting tempo preference strength. The influence of the variable tempo on their aesthetic judgment of the musical rhythms should temporarily decrease after inhibition of the left PMv and the stability of tempo preference should be transiently impaired.

In a randomly selected population, subjects considerably differ with regard to the strength of their tempo preference, with some subjects having no tempo preference at all and some subjects having a very strong tempo preference (Kornysheva et al., 2010). Subjects with a stronger tempo preference had a more pronounced PMv activity boost during rhythms with preferred tempo than subjects with weaker tempo preference, some of the latter even showing an activity decrease during preferred tempo (Fig. A.2). Accordingly, the effect of inhibitory stimulation was evaluated depending on the individual tempo preference strength. If PMv activity influences tempo preference, an inhibitory stimulation of this region should have a more pronounced effect on subjects with stronger in contrast to subjects with weaker tempo preference, in whom activity increase in the PMv tends to be lower or missing. rTMS over the left PMv should produce a more pronounced effect in subjects with strong tempo preference since these are assumed to show a larger activity increase in the left PMv under normal conditions (Fig. A.2). A temporary disruption of activity in the left PMv should reduce the strength of individual tempo preference more strongly in subjects with a pronounced tempo preference in a control session.

To ensure that the expected effect is both region-specific, specific to the function under investigation and bound to PMv stimulation in time, four controls were implemented: Firstly and based on the BOLD-contrast analysis of *Experiment 1*, the left temporo-occipital cortex/angular gyrus (AG) was chosen as a control site for stimulation. AG was significantly less activated (bilaterally) for all conditions containing auditory rhythms when compared to rest. Therefore, if the effect is specific to left PMv rather than just a region-unspecific influence of rTMS, the tendency to prefer a tempo shall be disrupted after left PMv stimulation, as compared to left AG stimulation (baseline). Secondly, the preference for a stimulus variable that is unrelated to timing within a sub-seconds range - timbre (spectro-temporal configuration of the sound) - served as a measure to probe the specificity of rTMS stimulation on tempo preference. Thirdly, a condition which measured tempo recognition (probability to recognize rhythms with a fast beat rate) throughout the experiment was included, thus controlling for more basic perceptual capacities. Finally, to ensure that the effect is bound to PMv stimulation, it was evaluated whether the effect is more pronounced in the first as compared to the second half of the experiment after PMv stimulation, since behavioral and neurophysiological effects of TMS are known to wear off across time (Allen et al., 2007; O'Shea et al., 2007).

7.2. Method

7.2.1. Participants

Sixteen healthy female volunteers (mean age 25.1, range 22-30 years) with normal or corrected to normal vision participated in *Experiment 2*. All subjects were right-handed according to the Edinburgh Inventory of Manual Preference (Oldfield, 1971). None of them were professional musicians. Their rhythm perception ability ranged from 22 to 29 (mean: 26.6; SE: 0.58) on a scale of 30 (online version of the rhythm test from the Montreal Battery of Evaluation of Amusia (MBEA), http://www.delosis.com/listening/home.html). Therefore, each subjects was within two standard deviations of the population mean (Peretz et al. (2003), cf. MBEA norms update 2008, http://www.brams.umontreal.ca/plab/publications/article/57). One additional subject participated in the experiment, but her results were excluded from further analysis due to an incorrect measurement of the resting motor threshold (cf. TMS protocol). All subjects were naïve concerning the hypothesis of this study and encountered the stimulus material for the first time. None of the subjects had any history of medical or psychiatric disease or contraindication to TMS (Wassermann, 1998). All subjects gave informed written consent to participate in *Experiment 2*. Experiments were approved by the Ethics Committee of the Medical Faculty, University of Cologne, Germany.

7.2.2. Stimuli and Tasks

Subjects were presented with auditory musical rhythms, which had five properties - tempo, measure (beat grouping), beat subdivision, rhythmic figure and timbre - that varied orthogonally on two or three levels, respectively (Fig. 7.1). These stimuli had been previously used and described in more detail in the *Experiment 1*.

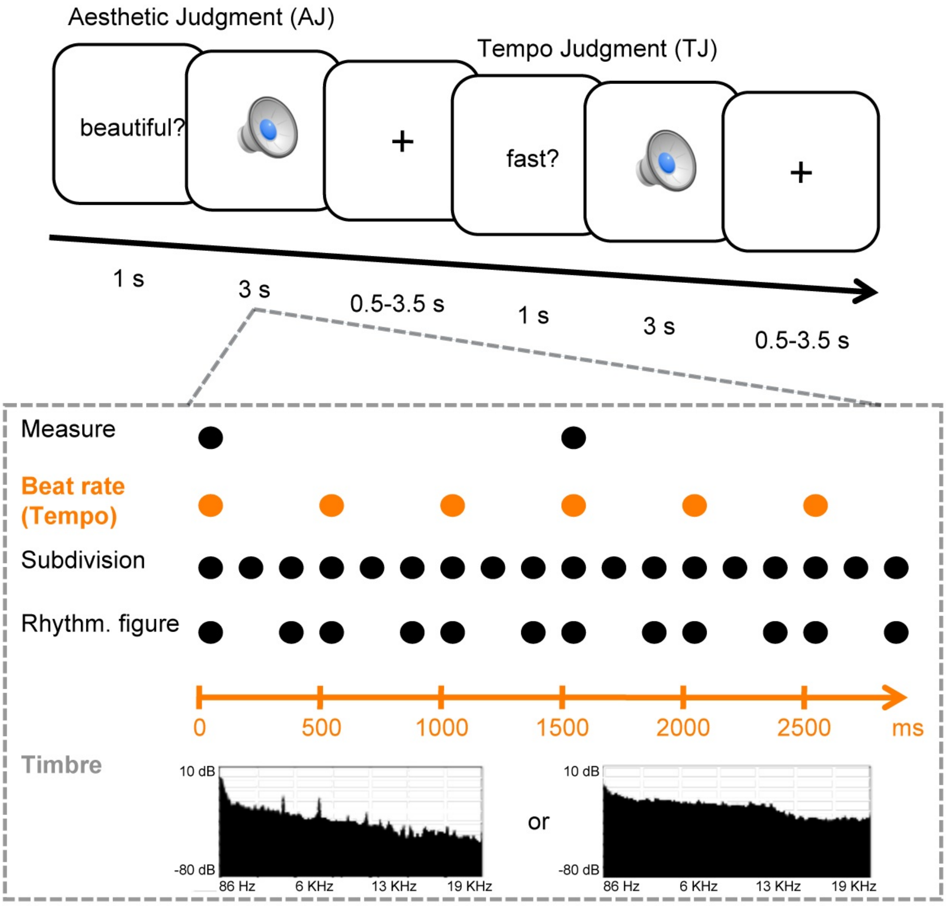


Figure 7.1.: *Experimental trial and stimulus structure. Each trial started with a variable jitter time of 0.5-3.5 s followed by a task cue (1 s) and an auditory stimulus presented for 3 s. Subjects were asked to decide whether or not the presented stimulus was beautiful (Aesthetic Judgment) or fast (Tempo Judgment). Participants were asked to press the selected response button when they had decided but still while the sound was presented. The auditory stimulus was determined by the factors beat rate (tempo/inter-onset-interval of beats), measure (the grouping of beats), beat subdivision (elements per beat), rhythmic figure and a factor unrelated to subseconds timing, timbre (spectro-temporal configuration of the sound stimulus), that varied on two or three levels respectively (cf. sound examples in Supplementary Material). Two of these five properties were relevant for the current experiment: beat rate (experimental variable in orange) and timbre (control variable in grey). The depicted rhythm example possesses a middle tempo with three beats per measure, three elements per beat and a repetitive rhythmic figure containing a long, followed by a short interval. The timbre panel shows two frequency spectrum types: sounds with predominantly wooden drum instruments (left side) and sounds with predominantly metallic drum instruments (right side).*

Two of these five properties were relevant for the current experiment: tempo (beat rate) and timbre (spectro-temporal configuration of the sound). Tempo was varied on three levels: slow (1.7 Hz / 100 BPM), middle (2.0 Hz / 120 BPM) and fast (2.5 Hz / 150 BPM), whereas timbre could be either ”wooden” (predominantly wooden drum instruments) or ”metallic” (predominantly metallic drum instruments) with two versions of each timbre. The assignment of these timbre versions to experimental conditions and sessions was counterbalanced across participants. In combination with the other three counterbalanced properties of the musical rhythms (beat subdivision, beat grouping, rhythmic figure), the rhythms appeared in all 216 possible permutations, each rhythm presented only once per session.

Musical rhythms were used for aesthetic (AJ) and tempo (TJ) judgment conditions, which were also included in the preceding *Experiment 1*. The participants were instructed to attend to the presented stimuli and decide whether or not the presented stimulus was beautiful (AJ) or fast (TJ) (7.1). As demonstrated in a post-experimental interview of the *Experiment 1*, the German word for ”beautiful”, ”schön”, which also means ”nice” and ”pleasant”, is closely related to liking the rhythms. The subjects were asked to judge the stimuli relative to other stimuli in the experiment and not relative to their favorite musical pieces. They were instructed to press the button as soon as they decided while the rhythm was presented. Loudness was adjusted individually.

Each trial (6 s) started with a cue (1 s), indicating whether to perform an aesthetic judgment (”beautiful?”) or a tempo judgment (”fast?”), followed by the stimulus (3 s) and a fixation phase the length of which was variable (0.5-3.5 s) depending on the jitter times (0, 500, 1000, or 1500 ms).

Since an inhibitory effect of rTMS usually does not outlast 20-30 minutes after the end of stimulation (Fitzgerald, et al. 2006), the experiment lasted 21.6 minutes, during which 216 trials were presented: 108 in the AJ and the TJ condition, respectively. To capture a possible recovery of tempo preference strength after rTMS during this time range (Allen et al., 2007; O'Shea et al., 2007), all levels of tempo and timbre were equally distributed across the two sub-blocks (10.8 minutes each; Fig. 7.2) and conditions, respectively. 16 different trial randomizations matching the above criteria were used.

7.2.3. Procedure

Each subject participated in two sessions that were separated by seven days, with an exception of two subjects, whose sessions were separated by eight and ten days, respectively. During the session the subjects were tested after rTMS over either the left PMv or the left AG (Fig. 7.2).

The order of the sessions was counterbalanced across participants. The experiment took place in a quiet, shaded and air-conditioned room. Subjects were comfortably seated in an adjustable armchair with a head-rest. Each session started with a training containing example trials (12 trials AJ and 12 trials TJ), which were randomly chosen from the pool of stimuli for each subject and counterbalanced for tempo and timbre. This training had the purpose to familiarize the subjects with the task and the musical rhythms, as well as the range of tempos. It has been suggested that the effects of brain stimulation depend on the initial state of the stimulated region (Siebner et al., 2004) and may be influenced by psychophysiological manipulations such as priming (Silvanto et al., 2008). When the level of excitation is high, a subsequent period of low frequency rTMS leads to a lasting reduction in excitability (Siebner et al., 2004). Therefore, this training also served to potentially enhance activity in the respective network involved in tempo preference and tempo recognition prior to the application of inhibitory rTMS.

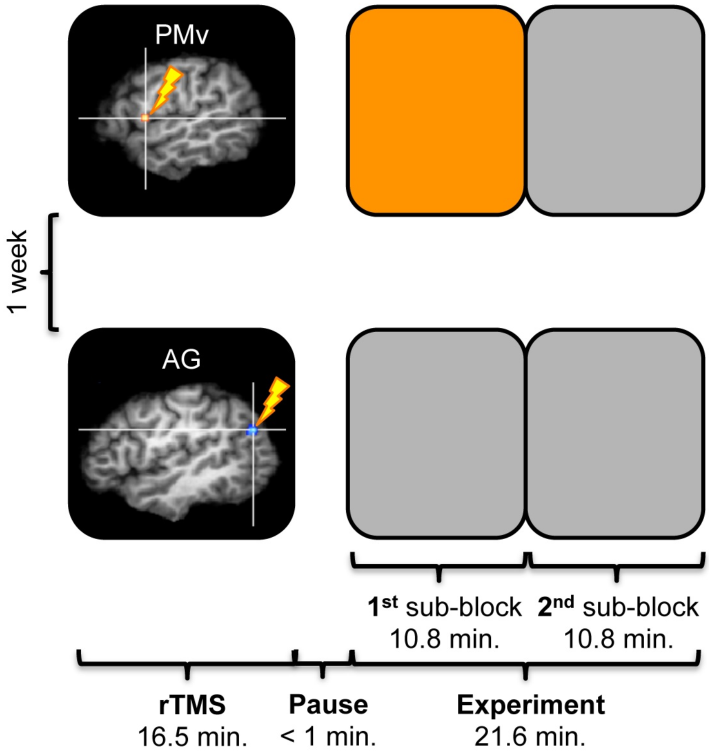


Figure 7.2.: *TMS session procedure. Offline 0.9 Hz rTMS was performed over the left ventral premotor cortex (PMv) and over a control region (left temporo-occipital cortex/angular gyrus (AG)) in two separate sessions with an interval of one week. Each stimulation protocol was followed by a 21.6 minute long experimental session that started within the first minute after stimulation. To capture a possible recovery of tempo preference strength after rTMS, the experiment consisted of two sub-blocks (10.8 minutes each).*

The subjects remained in the armchair after rTMS and were instructed not to talk during or after rTMS to minimize the interference of movement and speech with the hypothesized effect of the stimulation. The experiment started within the first minute after the administration of rTMS.

7.2.4. Site Localization

Stimulation targets were chosen on the basis of *Experiment 1* conducted with a different group of subjects. The PMv site was defined by the peak voxel activated in the left lateral premotor cortex for musical rhythms judged as beautiful and for musical rhythms with a preferred tempo (overlap of the contrasts beautiful versus not beautiful rhythms and preferred versus not preferred tempo in the aesthetic judgment condition; Talairach coordinate: -50 4 12; cf. Fig. 7.2A, upper part). The control site (AG) was defined by the peak voxel activated in the left inferior parietal cortex for rest against all conditions involving musical rhythms (Talairach coordinate: -44 -68 30; cf. Fig. 2A, lower part). The distance of the TMS coil to the left ear was approximately the same for the two target sites, ensuring a comparable amount of exposure to the TMS noise prior to the experiment. None of the subjects reported a difference between the sessions with regard to TMS noise intensity.

An individual high resolution T1-image (3D MDEFT, data matrix: 256 x 256 x 128) was acquired for each subject during a preceding scanning session. This 3D data set was transformed to Talairach stereotactic space (Talairach & Tournoux, 1988). The respective contrast images from *Experiment 1* were overlaid on each transformed individual 3D data set. The peak voxels were marked by crosshairs on the axial, coronal and sagittal planes, respectively. Subsequently, the stimulation targets were set manually on the T1-image according to the individual anatomical landmarks surrounding the crosshairs on the transformed 3D data set.

7.2.5. TMS stimulation

Stereotaxic frameless neuronavigation was obtained by the eXimia NBS system Version 2.1.1 (Nexstim, Helsinki, Finland). Coil tilting was tangential to the skull and current direction was perpendicular to the central sulcus. Online neuronavigation was used to maintain the targeted tilting and direction of the TMS coil across stimulation.

TMS was applied with a biphasic Nexstim Eximia TMS with a figure-of-eight-coil (diameter: 50 mm). Motor threshold was determined at each session prior to rTMS in the right first dorsal interosseus muscle. Electromyographic (EMG) signals were recorded by surface electrodes placed in a belly-tendon montage over the target muscle. The EMG signal was amplified, filtered with a 0.5 Hz high pass filter and digitized using a PowerLab 26 T Myograph and the ”Scope” software package Version 3 (ADInstruments Ltd, Dunedin, New Zealand). The resting motor threshold (RMT) was assessed by means of the maximum likelihood method as suggested by Awiszus (2003; TMS Motor Threshold Assessment Tool (MTAT) 2.0, Awiszus, F . and Borckardt, J.J., Brain Stimulation Laboratory, Medical University of South Carolina, USA, www.clinicalresearcher.org/software.htm, which has been suggested to be more accurate with the same number of stimuli (Awiszus, 2003; Awiszus et al., 1999; Mishory et al., 2004) in comparison to techniques proposed by Rossini et al. (1994), Rothwell et al. (1999) or Mills & Nithi (1997). Peak-to-peak amplitudes exceeding 50µV were regarded as motor evoked potentials.

Stimulation intensity was 90% of RMT, with a mean stimulation intensity of 37.8% (1.7% SE) of maximum stimulator output in the PMv and 39.0% (1.7% SE) in the AG session, the difference between the sessions being not significant (t = -0.977; p = .344, paired t-test). There was a significant correlation between the RMT in the two sessions (r = 0.74; p ¡ .01). For each of the sites stimulated, 900 pulses were applied at a frequency of 0.9 Hz (train duration 16.5 min). A stimulation frequency slightly below the standard 1 Hz stimulation was chosen to exclude potential interference of rTMS noise with the 2 Hz beat rate of the musical rhythms in the subsequent experiment (cf. Stimuli and Tasks).

7.2.6. Side effects of TMS

All 16 subjects reported muscular twitches in the left part of the face during the offline administration of rTMS over the left PMv. In contrast, only six subjects reported muscular twitches in the left part of the face during the offline administration of rTMS over the AG. At the end of the session with rTMS over the left PMv, one subject reported on a scale of 0 (”no”) to 10 (”worst possible”) a mild headache (2) and another subject reported a mild neck pain (1) in combination with a light nausea (1). At the end of the session with the administration of rTMS over the left AG two subjects reported a minor headache (3) in combination with a neck pain (2 and 5) and another subject reported light nausea (1). Prior to the session, the experimenter explicitly pointed out to each subject that they were free to terminate the stimulation or the experiment anytime as desired. However, no subjects terminated or paused the stimulation or the experiment, indicating that the above side-effects were not experienced as very pronounced. No other side-effects were reported by the subjects.

7.2.7. Behavioral analysis

For each individual participant, a linear mathematical model (individual case model) of judgment strategy was computed to examine the influence of the stimulus properties tempo and timbre on aesthetic judgments (Brehmer & Joyce, 1988; Cooksey, 1996; Jacobsen, 2004; Jacobsen et al., 2006; Kornysheva et al., 2010).

To this end, multiple regressions were computed using the enter method, including tempo (slow = ”1”, middle = ”2”, fast = ”3”) and timbre (”wooden” = ”1”, ”metallic” = ”2”) as potential predictors of individual performance in the aesthetic judgment condition (AJ) of each session and sub-block irrespective of the significance of their contribution. The latter one, being nominal, was assigned ”dummy” variables. The other three properties of the musical rhythms - measure or beat grouping, beat subdivision and rhythmic figure - were not included in the analysis. Note however, that the inclusion or exclusion of these properties as predictors in the regression (enter method) does not influence the results due to the orthogonality of all stimulus properties. This way, full models were computed to obtain the beta weights for the two predictors. These beta weights provided information on the mere tendency of every subject to prefer rhythms with slow (negative beta weights) or fast (positive beta weights) tempo, as well as rhythms with the timbre ”wooden” (negative beta weights) or ”metallic” (positive beta weights). The absolute value of beta weights for each session, as well as for each sub-block after rTMS was taken to reflect the strength of this preference (Kornysheva et al., 2010). For example, a subject would be given a high beta weight for tempo whenever the number of positive aesthetic judgments of rhythms with slow tempo exceeded the number of positive aesthetic judgments of rhythms with middle tempo, and the latter, in turn, exceeded the number of positive aesthetic judgments of rhythms with fast tempo, or the opposite direction. In contrast, the subjects gained a low beta weight, whenever the number of positive aesthetic judgments of rhythms with slow, middle and fast tempo was approximately equal.

The effect of inhibitory stimulation on tempo preference strength was evaluated by taking individual preference strength into account. Individual tempo preference strength was treated as a continuous variable, since inhibitory stimulation of the PMv should have a more pronounced effect on subjects with stronger preference, i.e. subjects who have been shown to have a greater PMv activity boost during rhythms with preferred tempo than subjects with no or weak tempo preference (Fig. A.2C). The following correlation analyses were computed using standard Pearson's correlation coefficient and significance to probe whether the effect of rTMS over the PMv (i) positively correlates with the individual tempo preference strength in the control session and (ii) whether this effect is transient, i.e. temporally bound to rTMS stimulation. To control for the functional specificity of this effect, the same analyses were performed for timbre preference (control variable), as well. Correlations between preference strength in the control session (beta weight following AG stimulation) and the behavioral effect of rTMS over the PMv (beta weight following AG stimulation minus beta weight following PMv stimulation) were computed. The behavioral effect of inhibitory PMv stimulation was analyzed for each of the two sub-blocks of 10.8 minutes following PMv stimulation.

Additionally, correlations between the preference strength for tempo in each sub-block of the the PMv and control sessions were computed. These correlations were used to investigate whether the stability of tempo preference strength within and across sessions is transiently impaired by PMv stimulation. As in the analyses above, the same correlations were also performed for timbre preference in order to evaluate the functional specificity of this effect. One-tailed correlations were used for experimental and control variables, since the hypotheses were unidirectional.

Individual tempo recognition during the tempo judgment condition (TJ) was computed for each session, as well as for each sub-block after rTMS, respectively. The performance was measured by the probability to recognize musical rhythms with a fast beat rate - the probability of recognition P(r) (Snodgrass & Corwin, 1988). The P(r) was defined as P(r) = HITS - FALSE ALARMS = (number of fast rhythms judged as ”fast” / number of fast rhythms) - (number of slow rhythms judged as ”fast” / number of slow rhythms).

A linear regression with the effect of PMv stimulation on tempo preference strength (beta weight for tempo following AG stimulation minus beta weight for tempo following PMv stimulation) as dependent and the effect on tempo recognition as independent variable (P(r) following AG stimulation minus P(r) following PMv stimulation) was computed. This was done in order to test whether the hypothesized effect on tempo preference strength could be explained by a disruption of tempo recognition.

Finally, reaction times and response distribution in the aesthetic and tempo judgment tasks were analyzed to control for possible confounds of rTMS over the PMv on attention, motor output and judgment bias.

7.3. Results

Preference strength for beat rate (tempo) and timbre

As expected on the basis of previous findings (Kornysheva et al. (2010), Fig. A.2C), the judgment analysis revealed that subjects differed with regard to the strength of their tempo preference, i.e., to how strongly tempo influenced their judgments, with absolute beta weights ranging from 0.05 (no tempo preference) to 0.64 (strong tempo preference) in the control session (rTMS over the left AG). The beta weight for tempo did not reach significance in three out of sixteen subjects (beta weights ranging from 0.05 to 0.16). The reduction of tempo preference after PMv stimulation was driven by subjects with strong tempo preference in the control session (after AG stimulation; baseline). The higher the subject's individual tempo preference strength in the control session, the more tempo preference strength was impaired after PMv stimulation ($r = .473^*$; $p = .03$). This effect of PMv stimulation was transient, i.e. temporally bound to the first sub-block (first 10.8 minutes) after PMv stimulation: Tempo preference strength in the control session (baseline) and

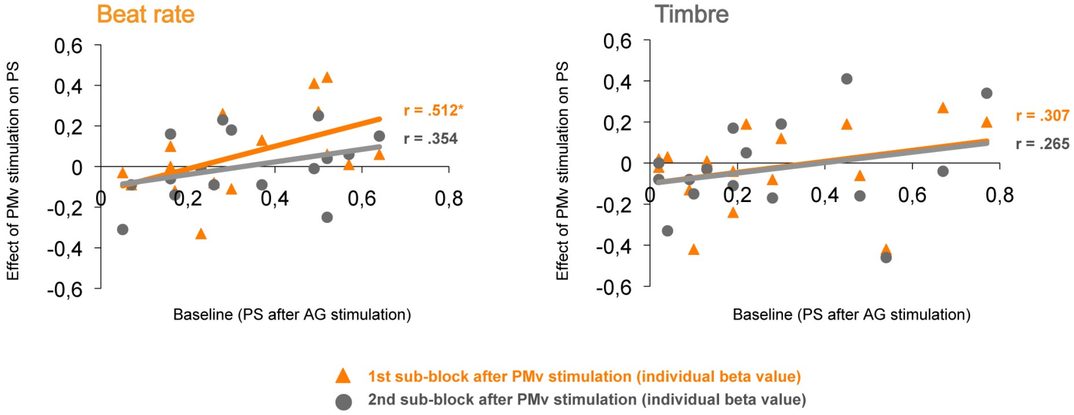


Figure 7.3.: *Influence of left PMv stimulation on tempo preference strength. The effect of inhibitory PMv stimulation on beat rate preference strength (rTMS over the left PMv minus rTMS over the control site) covaried positively with the baseline beat rate preference strength. A significant correlation occurred only in the first sub-block following rTMS over the left PMv. No significant correlation was observed for tone color. PS = preference strength.*

the effect of PMv stimulation on tempo preference strength correlated significantly in the first (r = .512*; p = .02), as opposed to the second sub-block following PMv stimulation (r = .354; p = .09) (Fig. 7.3, left part), consistent with an effect that wears off over time (Allen et al., 2007; O'Shea et al., 2007).

Serving as a control, the effect of PMv stimulation on preference strength for timbre was evaluated. As with regard to tempo preference, subjects differed in their preference strength for timbre, i.e. to how strongly timbre influenced their judgments. Beta weights ranged from 0.02 (no timbre preference) to 0.77 (strong timbre preference) in the control session. The beta weight for timbre did not reach significance in six out of sixteen subjects (beta weights ranging from 0.02 to 0.13). In contrast to the effect on tempo preference strength, a correlation analysis revealed that the effect of PMv stimulation on preference strength for timbre did not significantly increase depending on the individual preference strength for timbre in the control session, neither in the first sub-block (r = .307; p = .12), nor in the second sub-block (r = .265; p = .16) following PMv stimulation (Fig. 7.3, right part).

In line with the above results, the stability of individual preference strength within and across the PMv and AG sessions was selectively impaired for tempo preference strength in the first, but not the second sub-block following PMv stimulation: While timbre preference strength remained stable within and across sessions the stability of tempo preference strength was affected in the first sub-block following PMv stimulation (Table 7.1).

Table 7.1.: *Stability of preference strength for beat rate and timbre (control variable) within and across sessions. Correlation matrix shows Pearson's correlation coefficients and significance values (in parentheses). Significant coefficients are in bold font. The stability of beat rate preference strength within and across sessions was selectively impaired in the first sub-block following inhibitory PMv stimulation. Preference strength for timbre remained stable within and across sessions.*

Beat rate preference strength

		PMv		AG	
	sub-block	1st	2nd	1st	2nd
PMv	1st				
	2nd	.398			
		(.06)			
AG	1st	.302	**.546***		
		(.13)	(.01)		
	2nd	.389	**.693****	**.699****	
		(.07)	(.00)	(.00)	

Timbre preference strength

		PMv		AG	
	sub-block	1st	2nd	1st	2nd
PMv	1st				
	2nd	**.783****			
		(.00)			
AG	1st	**.644****	**.568***		
		(.00)	(.01)		
	2nd	**.563***	**.488***	**.654****	
		(.01)	(.03)	(.00)	

This pattern of effects confirms that tempo preference suppression was transient and thus related to inhibitory PMv stimulation. Note, that the session order was counterbalanced across subjects. Accordingly, the observed effects of rTMS over the left PMv on tempo preference could not be related to whether the PMv stimulation was administered on the first or the second session.

Beat rate recognition

Importantly, the disrupting effect on tempo preference in the first sub-block after stimulation could not be explained by an impairment of basic temporal perception: In a linear regression analysis, the effect of PMv stimulation on tempo recognition (1st sub-block) did not significantly predict the effect of PMv stimulation on individual tempo preference strength (1st sub-block) (R = .103; p = .71).

Reaction time

One subject had to be excluded from reaction time (RT) analysis, since the latency of one button was not recorded in the AG session. Mean response times and standard errors (in parentheses) in the AG session were as follows: beautiful (aesthetic judgment (AJ) ”yes”) 2016 ms (78 ms); and not beautiful (AJ ”no”) 1853 ms (87 ms); fast (tempo judgment (TJ) ”yes”) 1513 ms (78 ms); and slow (TJ ”no”) 1678 ms (81 ms). Mean response times in the PMv session were as follows: beautiful (AJ ”yes”) 2076 ms (88 ms); and not beautiful (AJ ”no”) 1848 ms (92 ms); fast (TJ ”yes”) 1525 ms (77 ms); and slow (TJ ”no”) 1677 ms (84 ms). A repeated-measures ANOVA over the judgment latencies with the factors ROI (PMv/AG), TASK (AJ/TJ), and TEMPO (slow/middle/fast) revealed a main effect of TASK (F(1,14) = 28,427, $p < .001$) due to longer RTs in AJ trials, a main effect of TEMPO (F(1,14) = 25,847, $p < .001$) due to longer RTs in trials with slow tempo. Notably, there was no main effect of ROI on reaction times (F(1,14) = 0,031, p = .86), suggesting that attention and motor output was comparable during measurements following PMv and AG stimulation.

Response distribution

Aesthetic judgment (AJ) showed 0.2% and tempo judgment (TJ) 0.1% non-responses. In the AG session, 45.4% of the stimuli under the aesthetic judgment task were judged as beautiful, 54.1% as not beautiful. In the PMv session, 42.5% of the stimuli under the aesthetic judgment task were judged as beautiful, 57.3% as not beautiful.

In the AG session, 53.5% of the stimuli under the tempo judgment task were judged as fast, 46.4% as not fast. In the PMv session, 50.5% of the stimuli under the tempo judgment task were judged as fast, 49.5% as not fast. There was neither a main effect nor an interaction with the factor ROI in a repeated-measures ANOVA over the percentage of judgments with the factors ROI (PMv/AG), TASK (AJ/TJ) and ANSWER (”yes”/”no”). There was a significant interaction of TASK and ANSWER due to the reduced fraction of answers ”yes”, i.e. ”beautiful” in the AJ task compared to the fraction of answers ”yes”, i.e. ”fast” in the TJ task (F(1,15) = 4,955, $p < .05$).

7.4. Discussion

Experiment 2 was conducted to determine whether the preference strength for a musical beat rate (tempo) would be affected after inhibitory stimulation of the left ventral premotor cortex (PMv). 0.9 Hz repetitive magnetic stimulation (rTMS) was used to temporarily reduce cortical excitability in the left PMv and measured the strength of the subjects' individual tempo preference in the first 21.5 minutes after stimulation. To control for the regional and functional specificity of rTMS, the baseline measurement was performed after stimulation over angular gyrus (AG) as a control site. Moreover, the preference strength for timbre and the overall tempo recognition were measured throughout the experiment. As hypothesized, rTMS over the left PMv compared to rTMS over the control site temporarily reduced the strength of individual tempo preference depending on how pronounced the tempo preference was in the control session. The disrupting effect of inhibitory left PMv stimulation correlated positively with the individual tempo preference strength in the baseline session, and wore off in the second part of the experiment following PMv stimulation. Likewise, the stability of tempo preference across the two sessions was impaired in the first sub-block after inhibitory PMv stimulation. Most importantly, both effects of rTMS over the left PMv were specific to the preference strength for tempo, whereas the preference strength for timbre, figuring as a control variable, was not affected. Finally, the effect on tempo preference strength was not related to a degradation of tempo perception itself.

Results suggest that a virtual lesion of the left PMv specifically interferes with the preference for beat rate as opposed to the preference for timbre, a timing-unrelated property of the musical rhythms employed here. These findings crucially extend the preceding fMRI results (Kornysheva et al., 2010) by showing that left PMv activity is affecting musical beat rate (tempo) preference.

It has been suggested that preference for a beat rate may be closely related to body movement. The tempo range of musical beat perception around 300-900 ms inter-onset-interval is similar to that of locomotion and other rhythmic movements (Fraisse, 1982; Moelants, 2003; Trainor, 2007). Accordingly, anthropomorphic features that affect locomotion factors were shown to be correlated with the preferred beat rate (Todd et al., 2007). In particular, the vestibular system, that is stimulated by head movement, has been suggested to be important with respect to beat preference: in both infants and adults active or passive movement (bouncing) compared to movement observation while listening to an ambiguous rhythm pattern has been shown to bias the perception of the ambiguous rhythm (Phillips-Silver & Trainor, 2005, 2007). Moreover, in adults passive motion of the head alone affected auditory encoding, whereas passive motion of legs did not (Phillips-Silver & Trainor, 2008). Evidence has been provided that a putatively homologous region of the human PMv in the macaque monkey sends direct cortico-fugal projections to the vestibular nuclei (Akbarian et al., 1993, 1994). At the same time, in humans, vestibular input has been shown to enhance BOLD-activity in ventral premotor regions (Lobel et al., 1998).

Additionally, the anatomical position of PMv renders this area a node for auditory-motor integration: According to current accounts, auditory information is transferred to premotor areas via the superior longitudinal and the arcuate fasciculus (AF), which connect the superior temporal and the inferior parietal lobe with the lateral precentral gyrus (Bernal & Ardila, 2009; Rilling et al., 2008; Saur et al., 2008) - the so-called dorsal auditory stream (Hickok & Poeppel, 2004, 2007; Rauschecker & Tian, 2000). A recent cortico-cortical evoked potential study has found that AF transmits information bidirectionally, i.e. also from precentral back to temporal and parietal regions (Matsumoto et al., 2004). These results challenge the traditional notion of a mono-directional posterior (auditory) to anterior (motor) flow of information of the AF (Geschwind, 1970), but advocate the notion that motor information is important for perception, as pointed out with respect to language (Liberman et al., 1967; Liberman & Whalen, 2000). Moreover, they are in line with findings demonstrating the influence of the motor on the sensory system by means of a corollary discharge or efference copy (Sperry, 1950; von Holst & Mittelstaedt, 1950), such as from the motor to the auditory systems in humans (Paus et al., 1996) and insect models (Poulet & Hedwig, 2006), as well as from motor to tactile (Blakemore et al., 2000, 1998) and from motor to visual systems (Wurtz, 2008). At the same time, the left PMv sends direct corticospinal outputs and projects to left primary motor cortex (Dum & Strick, 1991, 2002), as well as to its right homologue, the right PMv (Dancause et al., 2007).

In line with these anatomical findings, the PMv has been shown to be relevant for sensorimotor integration of auditory beat cues. Imaging studies revealed enhanced activation in PMv during the synchronization of finger tapping to an auditory beat (Jancke et al., 2000; Rao et al., 1997; Thaut, 2003). In contrast to the supplementary motor area (SMA), the PMv is specifically involved in the presence of externally cued beat. Studies, in which the underlying beat has to be internally generated on the basis of an auditory rhythmic structure (beat induction) have reported enhanced activation of the SMA and the putamen (Grahn, 2009; Grahn & Brett, 2007; Grahn & Rowe, 2009). Accordingly, in a recent study, Grahn & Brett (2009) has demonstrated that internal beat generation is impaired in Parkinson's disease (PD) patients compared to controls. Moreover, a therapeutic effect of synchronization to an externally cued beat on gait and speech has been reported in patients with PD, suggesting that the lateral premotor cortex compensates the functional impairment of the basal ganglia-SMA loop during voluntary movement (McIntosh et al., 1997; Thaut et al., 1999, 2001; Willems et al., 2007). Malcolm et al. (2008) examined the influence of 0.9 Hz rTMS over the PMv on the synchronization of finger tapping to a 2 Hz auditory beat. However, despite the increase in synchronization error after the stimulation of the PMv, this effect was not significant. Future studies should evaluate whether the absence of a significant effect with regard to synchronization is due to an effective compensation of PMv dysfunction by interconnected areas.

Moreover, recent structural and functional neuroimaging, as well as TMS studies, highlighted the importance of PMv in audiomotor integration of speech. It has been shown that adolescent and adult subjects with stuttering show a lower fractional anisotropy of white matter tracts underlying the PMv compared to healthy controls (Watkins et al., 2008). People with stuttering usually have expertise in using external timing cues like the pace of a metronome, other readers' speech in chorus reading, or altered auditory feedback to produce fluent speech (Alm, 2004; Buchel & Sommer, 2004). It has been suggested that in the presence of external timing cues the lateral premotor cortex and the cerebellum compensate for the dysfunctional basal ganglia-SMA loop, which fails to generate or appropriately transmit valid internal timing cues for movement and speech in people with stuttering, similar to PD patients (Alm, 2004). Thus, the reported structural abnormalities of white matter tracts underlying the lateral ventral premotor area may partly arise due to an altered gyrification of frontal and temporo-parietal areas in subjects with stuttering (Foundas et al., 2001). Apart from speech production, the PMv has been demonstrated to contribute to speech perception as well. Meister et al. (2007) found that low-frequency rTMS over the left PMv significantly impaired phonetic discrimination.

Can the involvement of the premotor cortex in the strength of beat rate preference be linked to the common urge to spontaneously tune in to a musical beat by toe tapping, swinging of the upper body, head nodding or humming? When considering the anatomical position of PMv and its function in auditory-motor integration, it is likely that auditory and vestibular input during repetitive movements around 2 Hz shape PMv connectivity, e.g. during walking, or motor synchronization to a musical beat. This connectivity in turn should determine the extent to which auditory rhythms with a particular beat rate cause activity in the PMv and thus the strength of beat rate preference. If PMv activity increase during rhythms with a preferred beat rate modulates activity in primary motor regions, it may be conceived to also drive the urge to tune-in to a musical beat by head nodding, toe tapping, humming etc. Alternatively, PMv activity influencing beat rate preference strength may reflect a perceptual phenomenon that does not affect auditory cued motor output. To address this question, future studies should probe the contribution of PMv activity on (effector-independent) synchronization to an auditory beat. Likewise, it is still an open question whether PMv activity during rhythms with a preferred beat rate is involved in a better prediction and / or an enhanced motor imagery of movements to the beat.

The current results indicate that the interference with tempo preference after rTMS over the left PMv could not be explained by an impairment of a more basic perceptual capacity of beat rate recognition, since the latter remained unaffected by rTMS. Although preceding fMRI findings implied that tempo preference and recognition drew on overlapping neural resources (*Experiment 1*), the current results suggest that beat rate recognition is subserved by a degenerate set of areas. TMS- or stroke-induced impairment of premotor and motor cortices automatically causes increased activity in the unaffected contralateral hemisphere, which in turn inhibits the affected hemisphere (Ferbert et al., 1992; Grefkes et al., 2008). Thus, it is possible that activity in the right PMv increased in response to TMS stimulation over the left PMv and successfully compensated for the disruption of left PMv activity during the tempo recognition task. This suggests that intact activity in the left PMv is not necessary for the tempo task. In contrast, the influence of tempo on the aesthetic judgments decreased after inhibitory stimulation of the left PMv. If an activity increase in the contralateral right PMv occurred, it still did not effectively compensate for this dysfunction. On the other hand, this dissociation may be driven by different task affordances with regard to the beat rate of musical rhythms. In the tempo in contrast to the aesthetic judgment condition, beat rate served as a primary cue. Tempo judgment relies on sensorimotor simulation of the external beat, whereas aesthetic judgment does not. Thus, it is conceivable that a disruption of PMv activity selectively engaged compensatory mechanisms during the tempo, but not during the aesthetic judgment task. Future studies should evaluate whether tempo preference is driven by a lateralized premotor component.

The disrupting effect of inhibitory left PMv stimulation on tempo preference strength was positively correlated with individual tempo preference strength in the control session. This result is in line with the previous finding which demonstrated that left PMv activity boost during preferred tempo correlates with individual tempo preference strength (Fig. A.2C). Subjects with a stronger activity increase in the left PMv during preferred tempo exhibited a more pronounced tempo preference. Thus, an interference with activity increase in this region by low-frequency rTMS produced an effect that co-varied positively with the subjects' baseline preference strength. Reducing cortical excitability in the left PMv by low-frequency rTMS demonstrated a stronger effect on these subjects.

The objective of *Experiment 2* was to test whether the left PMv activity affects tempo preference. Yet, it is feasible that other interconnected brain regions are equally critical for tempo preference. Since a TMS pulse can spread to connected sites, conditioning effects of rTMS may not be limited to the stimulated cortex, but give rise to functional changes in interconnected cortical areas (Lee et al., 2003; Paus et al., 1997), even when a stimulation intensity is below the individual motor threshold. Thus, it cannot be ruled out that rTMS over the left PMv additionally affected activity in interconnected cortical and subcortical regions. Future studies, in particular those that involve offline, as well as concurrent TMS and neuroimaging, should therefore dissociate the critical contribution of areas interconnected with the left PMv to tempo preference and, moreover, address the interaction between these areas during rhythm with individually preferred and not preferred tempo.

In conclusion, the results substantiate the influence of the left PMv on tempo preference and corroborate the preceding fMRI results. On the basis of current and prior behavioral, anatomical and neuroimaging findings, future studies should address whether activity increase in a subset of neurons of the ventral premotor cortex, a node of audiomotor integration, influences the urge to move or hum to a musical beat.

8. Experiment 3. H5-H7. Causal contribution of the PMv to auditory-motor synchronization and short-term reorganization after its disruption (rTMS-fMRI)

8.1. Introduction

An important research goal in basic and clinical neuroscience is to understand recovery of cognitive function. While some progress has been made in uncovering mechanisms of functional reorganization of motor, visuo-motor and partly speech recovery, compensatory mechanisms during auditory-motor integration remain largely unknown. Yet, the ability to accurately time movements on the basis of auditory input is essential in a variety of domains and situations, such as speech, singing and synchronizing to music, but also in environments with missing or only scarce visual information.

As a part of the dorsal auditory stream, the ventral premotor/frontal opercular region (PMv) has been shown to be a node for auditory-motor integration, specifically with regard to sequential auditory patterns like speech or music (Hickok & Poeppel, 2007; Zatorre et al., 2007; Rauschecker & Scott, 2009), in which timing is essential. Both its anatomical position and its functional properties suggest that this region may play a critical role in auditory-motor timing: The inferior portion of the PMv and the adjacent frontal operculum are reciprocally connected to auditory areas in the superior temporal gyrus via the arcuate fasciculus (AF) (Catani & Mesulam, 2008; Schubotz et al., 2010). Humans are known to have an enhanced AF compared to other primate species (Rilling et al., 2008) - a finding that strongly corresponds to the notion that humans are the only primate species exhibiting vocal learning and speech (Bernal & Ardila, 2009). In primates, the PMv has been shown to possess direct corticospinal outputs and project to the primary motor cortex via association fibres (Dum & Strick, 1991, 2002), as well as to its homologue, the contralateral PMv (Dancause et al., 2007).

The PMv has been proposed to provide a common platform for timing, both perceived and produced (Schubotz, 2007). The former is substantiated by neuroimaging studies involving sub-seconds temporal estimation (Coull et al., 2008; O'Reilly et al., 2008) and rhythmic sequence prediction tasks (Schubotz et al., 2000, 2003; Schubotz & von Cramon, 2001b; Wolfensteller et al., 2007; Chen et al., 2008); the latter by auditory-motor synchronization (Rao et al., 1997; Jancke et al., 2000; Thaut, 2003; Chen et al., 2009) and vocal imagery tasks (Wolfensteller et al., 2007; Riecker et al., 2000; Kleber et al., 2007). Accordingly, the PMv has been suggested to be a part of a network that enables sensorimotor feed-forward prediction of both self-generated (re-afferent), as well as externally-generated (ex-afferent) events in the sub-seconds range (Schubotz, 2007). However, other areas such as the PMd and the cerebellum have been associated with the above tasks (Chen et al., 2006; Olmo et al., 2007), as well, and the critical contribution of the PMv in auditory-motor timing is still under discussion (Zatorre et al., 2007).

In addition to the role of PMv in auditory-motor timing it remains unclear which degenerate set of brain areas may help to preserve auditory-motor timing performance following its disruption. Evidence from stroke and repetitive transcranial magnetic stimulation (rTMS) suggests that interhemispheric compensation may play an important role in motor, visuo-motor and speech recovery. However, this evidence is contradictive. Some studies report compensatory plasticity in the non-dominant hemisphere, when it comes to motor (Chollet et al., 1991), visuo-motor (O'Shea et al., 2007) and speech functions (Kell et al., 2009). Other, however, demonstrate that the contralesional hemisphere does not support behavioral compensation, and can even be maladaptive (Liepert et al., 2007; Grefkes et al., 2008; Nowak et al., 2008).

In *Experiment 3*, rTMS was combined with subsequent fMRI to examine the critical role of the left PMv in auditory-motor timing and investigate mechanisms of compensatory short-term functional reorganization that can reduce a negative behavioral effect of PMv interference. We hypothesized that rTMS over the left PMv (i) disrupts the accuracy of auditory-motor timing, (ii) triggers task-specific activity increase in the homologous right PMv, and that (iii) the latter effect is compensatory the higher the activity increase, the smaller the effect of left PMv stimulation across subjects.

Subjects had to synchronize left and right index finger tapping to the variable beat rate of auditory rhythms following rTMS over PMv as opposed to no rTMS. In accordance with (Repp, 2005), variation of tap-to-beat asynchrony, was taken as a measure of auditory-motor timing accuracy. To ensure that the behavioral change is not just an unspecific effect of rTMS, subjects also participated in a control session with rTMS over the left angular gyrus/parieto-occipital lobe (AG). To probe the functional specificity of rTMS, we assessed motor timing variability in a control task, in which subjects produced self-paced tapping to spectrally matched auditory stimuli, and evaluated measures related to motor output, overall auditory-motor coupling and attention to the task.

8.2. Methods

8.2.1. Subjects

Sixteen healthy volunteers (mean age 24.8, range 22-29 years, eight females) participated in the study. All subjects were right-handed according to the Edinburgh Inventory of Manual Preference (Oldfield, 1971). None of them were professional musicians. Their rhythm perception ability ranged from 23 to 30 (mean: 26.9; SE: 0.55) on a scale of 30 (online version of the rhythm test from the Montreal Battery of Evaluation of Amusia (MBEA), http://www.delosis.com/listening/home.html). Therefore, all subjects were within two standard deviations of the population mean (Peretz et al. (2003), cf. MBEA norms update 2008, http://www.brams.umontreal.ca/plab/publications/article/57). All subjects were naïve concerning the hypothesis of this study. However, 6 of 16 participants encountered the stimulus material for the second time, previously participating in a perceptual rhythm judgment experiment (Kornysheva et al., in press) or a perceptual rhythm judgment pilot. None of the subjects had any history of medical or psychiatric disease or contraindication to TMS (Wassermann, 1998; Rossi et al., 2009). All subjects gave informed written consent to participate in this study. Experiments were approved by the Ethics Committee of the Medical Faculty, University of Cologne, Germany.

8.2.2. Stimuli and Tasks

In the experimental condition, participants were presented with auditory musical rhythms consisting of drum sounds that were generated with the Microsoft Software Wavetable Synthesizer (GM drum map). Each auditory rhythm had five properties beat rate, measure (beat grouping), beat subdivision, rhythmic figure, and timbre that varied orthogonally on two or three levels, respectively (Fig. 8.1A).

These stimuli had been previously used and described in more detail in preceding studies (Kornysheva et al., 2010, in press). Beat rate, the external cue for finger tapping, was varied on three levels: slow (1.7 Hz / 100 beats per minute, BPM), middle (2.0 Hz / 120 BPM) and fast (2.5 Hz / 150 BPM). In combination with the other four counterbalanced properties of the musical rhythms (beat subdivision, beat grouping, rhythmic figure, timbre), there was a pool of 216 possible permutations. Each rhythm was encountered only once per session. Note that the factors beat grouping, beat subdivision, rhythmic figure and timbre were counterbalanced across beat rates, which means that they had no systematic effect on auditory-motor synchronization accuracy measured across beat rates. An important advantage of these types of stimuli is that in comparison to most studies that use isochronous metronome clicks for auditory-motor synchronization tasks, the current stimuli more closely resemble musical rhythms, and thus can be regarded as more ecologically valid cues for auditory-motor synchronization, while at the same time being experimentally controlled. Subjects had two tasks: a synchronization condition (SC) and a control condition (CC). In the SC they were instructed to tap to the respective periodic beat of the musical rhythm with the right or the left index finger according to the preceding cue (sinusoidal tone of either 400 or 1200 Hz,

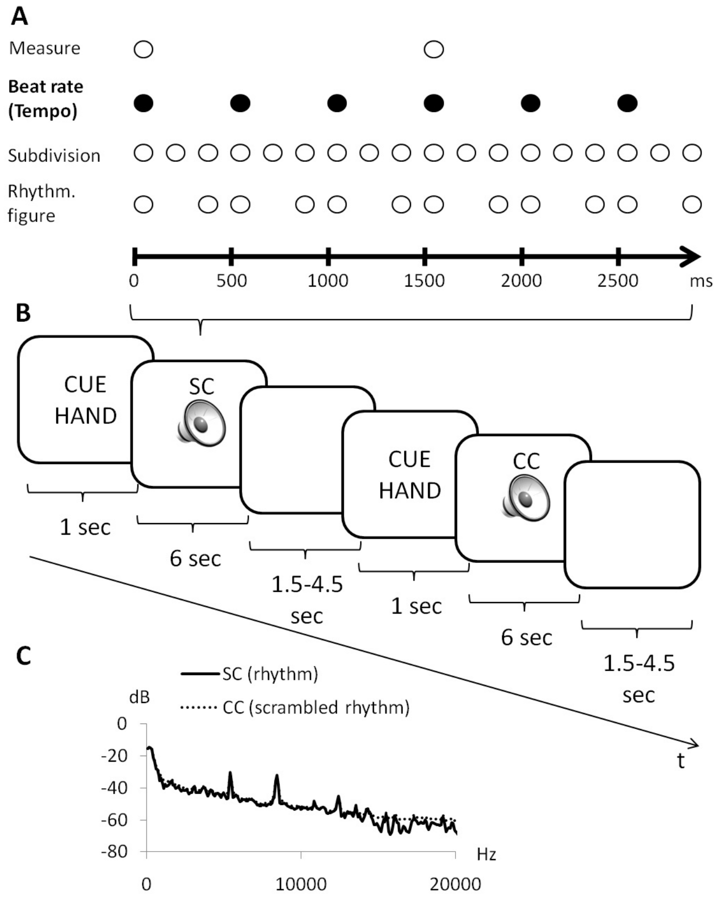


Figure 8.1.: *Stimulus material and trial structure. A: The auditory stimulus was determined by the factors beat rate (tempo/inter-onset-interval of beats; 1.7, 2.0 or 2.5 Hz), measure (the grouping of beats), beat subdivision (elements per beat), rhythmic figure and a factor unrelated to subseconds timing, timbre (spectro-temporal configuration of the sound stimulus), that varied on two or three levels respectively. Beat rate (filled circles) served as a cue for auditory-motor synchronization. The depicted rhythm example possesses a middle tempo with three beats per measure, three elements per beat and a repetitive rhythmic figure containing a long, followed by a short interval. B: Each trial started with an auditory cue (sinusoidal tone of either 400 or 1200 Hz, assignment counterbalanced across subjects), indicating whether to tap with the right or the left index finger, followed by the stimulus and a pause, which varied depending on the jitter times. In the synchronization condition (SC) subjects were instructed to tap to the respective periodic beat of the musical rhythm with the right or the left index finger according to the preceding cue. In CC subjects were presented with scrambled versions of musical rhythms (randomized 10 ms segments of the respective rhythms). The subjects task was to tap regularly in a self-paced manner. C: The spectrum of the scrambled rhythms in CC closely matched that of the rhythms in the SC; cf. trial examples in Supplementary material.*

assignment counterbalanced across subjects). In the CC they were presented with scrambled versions of musical rhythms (randomized 10 ms segments of the respective rhythms), which spectrally closely matched the stimuli in the SC (Fig. 8.1C), but lacked beat or any other type of a regular temporal organization. The subjects task was to tap regularly in a self-paced manner, with the right or the left index finger according to the cue at the beginning of the trial. On the behavioral level, the CC served to evaluate motor timing, as opposed to auditory-motor timing. On the fMRI level, the CC served to subtract out spectral acoustic input, as well as motor output, hence allowing to isolate activation related to auditory-motor timing by comparison between SC and CC. Cues for left and right finger tapping were equally distributed across SC and CC trials.

Each trial (10 s) started with an auditory cue (1 s), indicating whether to tap with the right or the left index finger, followed by the stimulus (6 s) and a pause, the length of which was variable (0.5-3.5 s) depending on the jitter times (0, 500, 1000, or 1500 ms; Fig. 8.1B).

Since an inhibitory effect of rTMS usually does not outlast 20-30 minutes after the end of stimulation (Fitzgerald et al., 2006), the experiment lasted 20 minutes, during which 120 trials were presented in a pseudorandom fashion: 54 in the SC and the CC condition, respectively, as well as 12 in the resting condition (RC). To capture a possible recovery of synchronization accuracy after rTMS during this time range (O'Shea et al., 2007; Allen et al., 2007) all conditions and levels of tempo and timbre were equally distributed across each of the four sub-blocks of 5 minutes, respectively. We used 4 different trial randomizations matching the above criteria.

8.2.3. Procedure

All sixteen subjects participated in two rTMS-fMRI sessions with rTMS over either the left PMv or the left AG (rTMS control), respectively. The PMv and AG sessions were carried out at one-week intervals and their order was counterbalanced across participants. Each subject practiced the task directly prior to the first rTMS-fMRI session and practice was refreshed briefly prior to the second session. Each session started with a training containing example trials (9 trials SC and 9 trials CC), which were randomly chosen from the pool of stimuli for each subject and counterbalanced for tempo. This training had the purpose to familiarize the subjects with the task and the musical rhythms, as well as the range of tempos.

During each session subjects underwent two fMRI scans, one of which was preceded by 0.9 Hz rTMS over either the left PMv or the left AG. To exclude a learning effect, the scan order was counterbalanced across rTMS-sites and participants: In half of the subjects and sessions, respectively, the fMRI scan following rTMS came first (Fig. 8.2C). In this case, the second fMRI scan was performed following a 45 minutes interval, during which the subjects stayed in a room adjacent to the MRI scanner room. The four scans will are referred to as follows: ”PMv TMS” (scan directly preceded by rTMS over PMv), ”PMv no TMS” (scan not directly preceded by rTMS over PMv), ”AG TMS” (scan directly preceded by rTMS over AG), ”AG no TMS” (scan not directly preceded by rTMS over AG).

The fMRI scan following rTMS started 3:34 min (SE 0:07) after the end of PMv stimulation and 3:16 min (SE 0:03) after the end of AG stimulation. The 18 s difference between the PMv and AG sessions was significant ($t = 2.6$; $p < .05$, paired t-test). However, since fMRI after PMv stimulation started later than after AG, a possible effect of PMv stimulation on behavior or BOLD signal cannot be explained by a temporal proximity and stronger influence of rTMS. During the in-

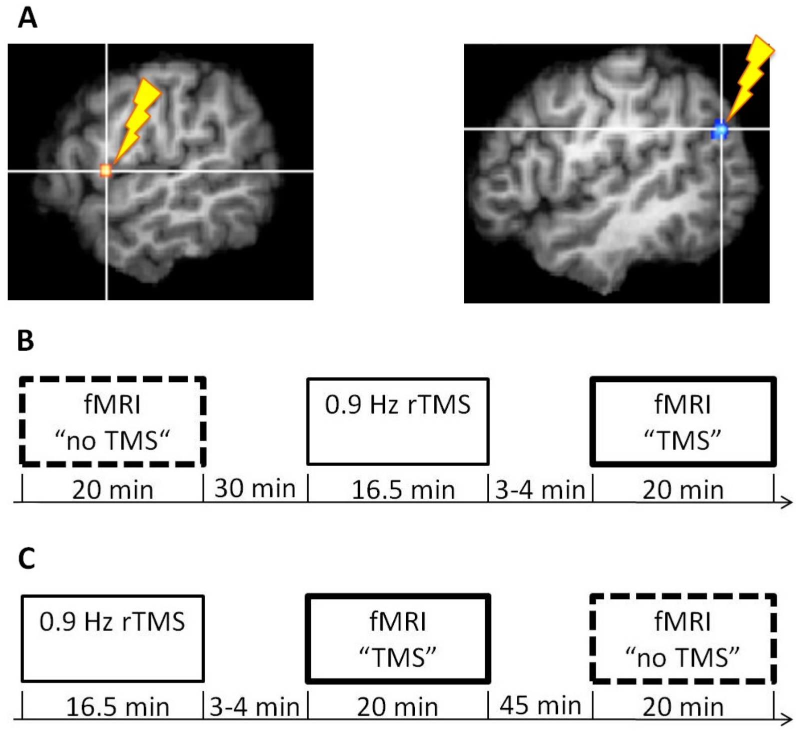


Figure 8.2.: *Stimulation sites and session procedure. A: Each subject participated in two rTMS-fMRI sessions separated by one week, in which rTMS was performed either over the left PMv or the left AG (rTMS control), respectively. The stimulation sites were chosen on the basis of Kornysheva et al. (2010). B: In one half of the subjects, each session started with an fMRI scan not preceded by rTMS ("fMRI no TMS" first), C: in the other half the fMRI scan following rTMS came first ("fMRI TMS" first). In the latter case, the second fMRI scan ("no TMS") was performed following a 45 minutes interval, during which the subjects stayed in a room adjacent to the MRI scanner room.*

terval between the end of rTMS and the beginning of the fMRI scan, subjects were asked to interact with the experimenters as little as possible. They were moved with a wheelchair to the adjacent MRI scanner room and were only required to get onto the scanner bed.

8.2.4. Site localization

Stimulation targets (8.2A) were chosen on the basis *Experiment 1* that involved the same auditory rhythms and was conducted with a different group of subjects. The PMv site was defined by the peak voxel in the left ventral premotor cortex (PMv) activated during auditory rhythms with preferred beat rate, as well as during a beat rate (tempo) judgment task (Talairach coordinate: -50 4 12). The control site (AG) was defined by the peak voxel activated in the left inferior parietal cortex for rest against all conditions involving musical rhythms (Talairach coordinate: -44 -68 30). The distance of the TMS coil to the left ear was approximately the same for the two target sites, ensuring a comparable amount of exposure to the TMS noise prior to the experiment. None of the subjects reported a difference between the sessions with regard to TMS noise intensity.

An individual high resolution T1-image (3D MDEFT, data matrix: 256 x 256 x 128) was acquired for each subject during a preceding scanning session. This 3D data set was transformed to Talairach stereotactic space (Talairach & Tournoux, 1988). The respective contrast images from the preceding fMRI study were overlaid on each transformed individual 3D data set. The peak voxels were marked by crosshairs on the axial, coronal and sagittal planes, respectively. Subsequently, the stimulation targets were set manually on the T1-image according to the individual anatomical landmarks surrounding the crosshairs on the transformed 3D data set.

8.2.5. TMS stimulation

Stereotaxic frameless neuronavigation was obtained by the eXimia NBS system Version 2.1.1 (Nexstim, Helsinki, Finland). Coil tilting was tangential to the skull and current direction was perpendicular to the central sulcus. Online neuronavigation was used to maintain the targeted tilting and direction of the TMS coil across stimulation.

TMS was applied with a biphasic Nexstim Eximia TMS with a figure-of-eight-coil (diameter: 50 mm). Motor threshold was determined at each session prior to rTMS in the right first dorsal interosseus muscle. Electromyographic (EMG) signals were recorded by surface electrodes placed in a belly-tendon montage over the target muscle. The EMG signal was amplified, filtered with a 0.5 Hz high pass filter and digitized using a PowerLab 26 T Myograph and the ”Scope” software package Version 3 (ADInstruments Ltd, Dunedin, New Zealand). The resting motor threshold (RMT) was assessed by means of the maximum likelihood method as suggested by Awiszus (2003; TMS Motor Threshold Assessment Tool (MTAT) 2.0, Awiszus, F. and Borckardt, J.J., Brain Stimulation Laboratory, Medical University of South Carolina, USA, http://www.clinicalresearcher.org/software.htm), which has been suggested to be more accurate with the same number of stimuli (Awiszus, 2003; Awiszus et al., 1999; Mishory et al., 2004) in comparison to techniques proposed by Rossini et al. (1994), Rothwell et al. (1999) or Mills & Nithi (1997). Peak-to-peak amplitudes exceeding 50µV were regarded as motor evoked potentials.

Stimulation intensity was 90% of the individual resting motor threshold (RMT), with a mean stimulation intensity of 33.6% (1.6% SE) of maximum stimulator output in the PMv session and 35.1% (2.1% SE) in the AG session, the difference between the sessions being not significant (t = -1.5; p = .19, paired-samples t-test).

There was a significant correlation between the RMT in the two sessions (r = 0.89; p ¡ .001). For each of the sites stimulated, 900 pulses were applied at a frequency of 0.9 Hz (train duration 16.5 min). A stimulation frequency slightly below the standard 1 Hz stimulation was chosen to exclude potential interference of rTMS noise with the 2 Hz beat rate of the musical rhythms in the subsequent experiment (cf. Stimuli and Tasks).

8.2.6. Behavioral analysis

Coefficient of variation (CV) in the synchronization condition (SC)

In the SC the subjects were instructed to synchronize their taps to the beat of the presented auditory rhythms. To assess the effect of TMS on auditory-motor timing variability, the coefficient of variation CV was computed with regard to the tap-to-beat asynchrony across SC trials. CV of absolute tap-to-beat asynchrony A across SC trials was defined as follows: $CV_{sc} = \frac{A_{SDsc}}{A_{MEANsc}}$. To make asynchrony comparable across rhythms with different beat rates, the absolute asynchrony A_i of each tap onset T_i minus the beat onset B_i was calculated as percent of inter-onset-interval (IOI) of consecutive beats: $A_i = \frac{|T_i - B_i|}{IOI} * 100$. Average asynchrony A in percent IOI was calculated for each SC trial. Subsequently, CV_{sc} was determined across trials of each scan, as well as each sub-block of five minutes as outlined above. Taps within the boundary of $\pm 40\%$ of the respective IOI around the beat onset were considered. This relatively wide criterion was chosen to account for the hypothesized increase in variability of asynchrony after rTMS over the left PMv. Only tap asynchronies relative to the third and following beats in each trial were taken into consideration, since a minimum of two consecutive beats is necessary to extrapolate the beat rate of an isochronous cue.

To probe the hypothesis that synchronization accuracy will be impaired, i.e. CV_{sc}

will increase, after PMv stimulation, a one-tailed paired-samples t-test with ”PMv TMS” compared to ”PMv no TMS” was performed. The same test was conducted for ”AG TMS” compared to ”AG no TMS”, to examine the regional specificity of rTMS. To evaluate time-dependent effects, an ANOVA with the factors TMS (no tms/ tms) by TIME (1st/ 2nd/ 3rd/ 4th sub-block) was performed for the PMv session, as well as for the AG session. If significant interactions between TMS and TIME were present, post-hoc Bonferroni corrected t-tests were computed for CV in TMS and no TMS scans within each sub-block.

Coefficient of variation (CV) in the control condition (CC)

In the CC the subjects were instructed to produce regular self-paced tapping to scrambled rhythms. To assess the effect of TMS on motor timing variability, the CV_{cc} was computed with regard to the tap-to-tap' asynchrony across CC trials where tap' T_{ii} is the expected time at which a tap T_i should occur according to the mean inter-tap-interval ITI_{mean} during the respective scrambled rhythm. The mean inter-tap-interval ITImean was calculated as follows: $ITI_{mean} = \frac{T_n - T_3}{n}$, where n is the number of taps occurring in the time between the third tap T_3 and the last tap T_n during the presentation of the scrambled rhythm. The onset T_{ii} of each expected tap occurring between the third tap T_3 and the last tap T_n were calculated as $T_{ii} = T_3 + ii * ITI_{mean}$. CV of absolute tap-to-tap' asynchrony A across trials in the CC was defined as follows: $CV_{cc} = \frac{A_{SDcc}}{A_{MEANcc}}$.

To make tap-to-tap' asynchrony comparable across CC trials with different regular self-paced tapping rates, the absolute asynchrony A_{ii} of each actual tap onset of T_i minus the expected tap onset T_{ii} was calculated as percent of the respective ITI_{mean}: $A_{ii} = \frac{|T_i - T_{ii}|}{ITI_{mean}} * 100$.

Note that this procedure is analogous to calculation of asynchrony A_i in the synchronization condition (SC) which takes into account the respective inter-onset-interval (IOI) of consecutive beats. Average asynchrony A in percent ITI_{mean} was calculated for each CC trial. Subsequently, CV_{cc} was determined across trials of each scan minutes as outlined above. Analogous to the CV calculation in the SC task, the first two taps in each trial were excluded from further analysis. Only taps within the boundary of ±40% of the respective ITI_{mean} around the expected T_{ii} onset were considered.

To evaluate a directional effect of PMv rTMS on CV in the control condition (CC), a one-tailed paired-samples t-test with ”PMv TMS” compared to ”PMv no TMS” was performed, as in the SC. To examine the regional specificity of a potential rTMS effect on motor variability in the CC, the same test was conducted for ”AG TMS” compared to ”AG no TMS”.

Tapping rate

Tapping rate was computed to control for differences in motor output between scans preceded or not preceded by rTMS. It was calculated by considering the overall number of taps per stimulus duration (6 sec) and was averaged across trials in each scan. To examine whether the subjects adjusted their tapping rate to the respective beat rate in the SC task independent of TMS sessions, an ANOVA with the factors TMS (tms/ no tms) and BEAT RATE (1.7/2.0/2.5 Hz) was performed.

Error rate

SC and CC trials that contained at least one tap executed with an incorrect effector, i.e. a left finger tap when right finger tapping was cued at trial onset and vice versa, were used to compute the effector error rate as percent of all trials. As in the imaging data analysis, these trials were excluded from further statistics.

8.2.7. MRI data acquisition

Imaging was performed at a 3 T scanner (Siemens TRIO, Erlangen, Germany) equipped with a standard birdcage head coil. Participants were placed on the scanner bed in a supine position with their right and left index fingers positioned on a response button of the left and right response box. To prevent postural adjustments, the participants' arms and hands were carefully stabilized by supporting form-fitting cushions. Additional form-fitting cushions were utilized to prevent head and arm movements. Rhythms were presented over Nordic Neurolab AudioSystem headphones with 30dB headset gradient noise attenuation. Further attenuation was achieved with insert earplugs rated to attenuate scanner noise by approximately 38 dB. Thirty axial slices (210 mm field of view, 64 x 64 pixel matrix, 4 mm thickness; 1 mm spacing, in-plane resolution of 3.28 x 3.28 mm) positioned parallel to the bicomissural plane (AC-PC) covering the whole brain were acquired using a single-shot gradient echo-planar imaging (EPI) sequence (TE 30 ms, flip angle 90°, TR 2000 ms, 156.2 kHz acquisition bandwidth) sensitive to blood oxygenation level-dependent (BOLD) contrast. In total, 620 functional images were acquired in each single run. Prior to the functional imaging, 30 two-dimensional anatomical T1-weighted MDEFT images and 30 T1-weighted EPI images with the same spatial orientation as the functional data were acquired. The EPI acquisition was continuous to prevent periodic silent gaps between TRs to disrupt the participants encoding of the rhythms. A slice acquisition frequency of 15 Hz was chosen to ensure the continuous scanner noise to be well above the fastest frequency of elements of the rhythmical stimuli beat subdivision (12.5 Hz) to prevent an auditory interaction between the two sources of rhythmic patterns and ensure that the participants were able to attend to the stimuli. By conducting a short auditory test with the EPI sequence prior to data acquisition the sound level was adjusted for each participant in such a way that the stimuli could be easily heard over the scanner noise by each participant at an individually comfortable sound pressure level. When explicitly asked in a post experimental interview, participants reported no difficulty hearing the stimuli during the whole course of the measurement or performing any of the tasks.

8.2.8. MRI data analysis

Functional data were motion-corrected online with the Siemens motion correction protocol (Siemens, Erlangen, Germany). Further processing of the fMRI data was performed using the software package LIPSIA (Lohmann et al., 2001). To correct for the temporal offset between the slices acquired in one image, a cubic-spline interpolation was employed. Low-frequency signal changes and baseline drifts were removed using a temporal highpass filter with a cutoff frequency of 1/96 Hz. Spatial smoothing was performed with a Gaussian filter of 5.65 mm FWHM. To align the functional data slices with a 3D stereotactic coordinate reference system, a rigid linear registration with six degrees of freedom (3 rotational, 3 translational) was performed. The rotational and translational parameters were acquired on the basis of the MDEFT (Norris, 2000) and EPI-T1 slices to achieve an optimal match between these slices and the individual 3D reference data set. This 3D reference data set was acquired for each subject during a previous scanning session. The MDEFT volume data set with 160 slices and 1mm slice thickness was standardized to the Talairach stereotactic space (Talairach & Tournoux, 1988). The rotational and translational parameters were subsequently transformed by linear scaling to a standard size. The resulting parameters were then used to transform the functional slices using trilinear interpolation, so that the resulting functional slices were aligned with the stereotactic coordinate system, thus generating output data with a spatial resolution of 3 x 3 x 3 mm (27 mm^3). The statistical evaluation was based on a least-squares estimation using the general linear model for serially autocorrelated observations (Friston, 1994; Friston et al., 1995a,b; Worsley & Friston, 1995). The design matrix was generated with a synthetic hemodynamic response function (Friston et al., 1998;

Josephs et al., 1997) and its first derivative modeled at the onset of the stimuli and at trial onset in the resting condition. Only trials in which all taps were performed with the correct effector according to cue (right or left hand, respectively) were included in the analysis. The number of taps during each stimulus was included as a regressor of no interest to control for differences between the number of taps in SC and CC. The model equation, including the observation data, the design matrix and the error term, was convolved with a Gaussian kernel of dispersion of 4 s FWHM to deal with the temporal autocorrelation (Worsley & Friston, 1995). In the following, contrast-images, i.e. beta value estimates of the raw-score differences between specified conditions, were generated for each participant. As noted before, each individual functional dataset was aligned with the standard stereotactic reference space, so that a group analysis based on the contrast-images could be performed. A one-sample t-test was employed for the group analyses across the contrast images of all subjects (SC vs. CC) for each scan separately, which indicated whether observed differences between the two conditions were significantly distinct from zero. In addition, paired t-test of the same contrast images was performed to obtain statistical significance of pairwise comparisons between PMv TMS vs. PMv no TMS, PMv TMS vs. AG TMS, PMv TMS vs. AG no TMS. T values were subsequently transformed to Z scores. To compute the common activation increases in the above contrasts, a conjunction (Nichols et al., 2005) between the contrasts SC vs. CC in all scans, as well as between all pairwise comparisons was performed. Note that, since the current study is the first to evaluate short-term reorganization of the auditory motor integration network after rTMS, whole brain analysis were performed since our aim was to identify areas with a potential compensatory mechanism in addition to our hypothesis with regard to the role of the right PMv after rTMS of the left PMv.

To correct for false-positive results, in a first step, the initial voxelwise z-threshold was set to Z = 2.576 (p = .005, uncorrected) for the conjunction of the main contrast SC vs. CC across all scans, as well as Z = 2.33 (p=.01, uncorrected) for the conjunction of pairwise comparisons. In a second step, the results were corrected for multiple comparisons using cluster-size and cluster-value thresholds obtained by Monte-Carlo simulations at a significance level of p<.05. Based on our a priori hypothesis, activity increase in the right PMv after rTMS over the left PMv is reported on the basis of thresholded Z = 2.33 (p=.01), but uncorrected conjunction of the pairwise comparisons.

Additionally, percent signal change was analyzed in several functionally defined regions of interest (ROIs). A ROI was defined as the peak voxel and a sphere of six adjacent voxels in regions of the dorsal auditory stream the left PMv and the left STG that was activated relatively more for SC vs. CC, as well as in regions with significant activity increase after rTMS over the left PMv compared to all other scans right PMv and cerebellar vermal lobule V. Within each ROI, the percentage signal change was calculated in relation to the mean signal intensity across all time steps of the respective scan and for each of the four five-minute sub-blocks to examine effects that change over time. Subsequently, the mean signal change over a 6 s epoch, starting 4 s after stimulus onset, was extracted for each condition and participant. To probe the compensatory nature of the activity enhancements after left PMv stimulation and determine the compensatory significance of these enhancements across time, multiple regression analyses were computed using the stepwise method for the respective ROIs, including individual percent signal increase for auditory-motor timing (SC minus CC) during each of the four five-minute sub-blocks after rTMS as potential predictors of the individual behavioral effect of rTMS (CV in TMS minus no TMS in the respective scan). Significant standardized regression coefficients are reported to assess the presence of an inverse relationship between the behavioral effect of rTMS and the activity increase for SC vs. CC after rTMS which would suggest a compensatory activity increase. Note that only predictors providing incremental explanation of behavioral variance (P-values 0.05) entered the stepwise multiple regression model. The anatomical locations of the functional activation were assigned by considering both the peak voxel and the position of the respective activation cluster on the mean brain of the 16 subjects transformed in Talairach stereotaxic space (Talairach & Tournoux, 1988). The MRI atlas of the cerebellum by Schmahmann et al. (2000) was used to locate cerebellar activations.

8.3. Results

8.3.1. Behavioral results

Effect on auditory-motor timing: Coefficient of variation in the synchronization condition (SC)

The coefficient of variation (CV) of tap-to-beat asynchrony across trials was taken as a measure of synchronization accuracy in accordance with Repp (2005). As hypothesized, a one-tailed paired samples t-test between CV in ”PMv no TMS” and ”PMv TMS” revealed a significant increase of CV after left PMv stimulation (t(15) = -1.78, $p < .05$; (Fig. 8.3A). In contrast, a one-tailed paired samples t-test between the coefficient of variability (CV) in ”AG no TMS” and ”AG TMS” showed no significant increase of CV after left PMv stimulation (t(15) = -0.46, p = .33; Fig. 8.3A). To evaluate whether this effect was most pronounced in the first minutes following rTMS, an ANOVA with the factors TMS (no tms/ tms) by TIME (1st/ 2nd/ 3rd/ 4th sub-block) was computed for each session. There was a significant interaction between the two factors in the PMv session (F(3,45) = 3.20, $p < .05$), with a significant difference between ”PMv no TMS” and ”PMv TMS” in the first sub-block only (t(15) = -4.476, $p < .01$, Bonferroni corrected; Fig. 8.3B).

No significant interaction of TMS by TIME was found in the AG session (F(3,45) = 0.01, p = .850; Fig. 8.3B).

Control 1 - Effect on motor timing: Coefficient of variability in the control condition (CC)

To ensure that this effect was related to auditory-motor timing and not just to motor timing variability, CV of tap-to-tap' asynchrony was computed in the control condition (CC), in which subject produced regular self-paced tapping during an auditory stimulus, that spectrally matched the auditory rhythms, where tap is the time at which a tap should have occurred according to the mean inter-tap-interval in the respective trial (cf. Methods). In contrast to CV of tap-to-beat asynchrony in the SC condition, a one-tailed paired samples t-test between the CV of tap-to-tap' asynchrony in CC in ”PMv no TMS” and ”PMv TMS” showed no significant increase after left PMv stimulation (t(15) = -0.21, p = .49; Fig. 8.3C). Likewise, a one-tailed paired samples t-test between the CV of tap-to-tap' asynchrony in ”AG no TMS” and ”AG TMS” showed no significant increase after ”AG TMS” in CC, (t(15) = 0.40, p = .35; Fig. 8.3C).

Control 2 - Effect on motor output and on auditory-motor coupling: Tapping rate

Stimulation of the PMv might have potentially impaired primary motor function due to the possibility of stimulation spreading to primary motor cortex. To control for differences in motor output depending on the TMS session, the overall tapping rate was assessed for each session. No differences were revealed by one-tailed paired samples t-tests between no TMS and TMS with regard to tapping rate in SC or CC trials, neither in the PMv, nor in the AG sessions (Fig. 8.3D, left side). If rTMS had an influence on the overall coupling of the subjects tapping rate to the auditory beat rate which could change from one SC trial to the next, they would be impaired in adjusting their tapping frequency to the beat rate of the respective rhythmic stimulus. However, an ANOVA with the factors TMS (no tms/ tms) and BEAT

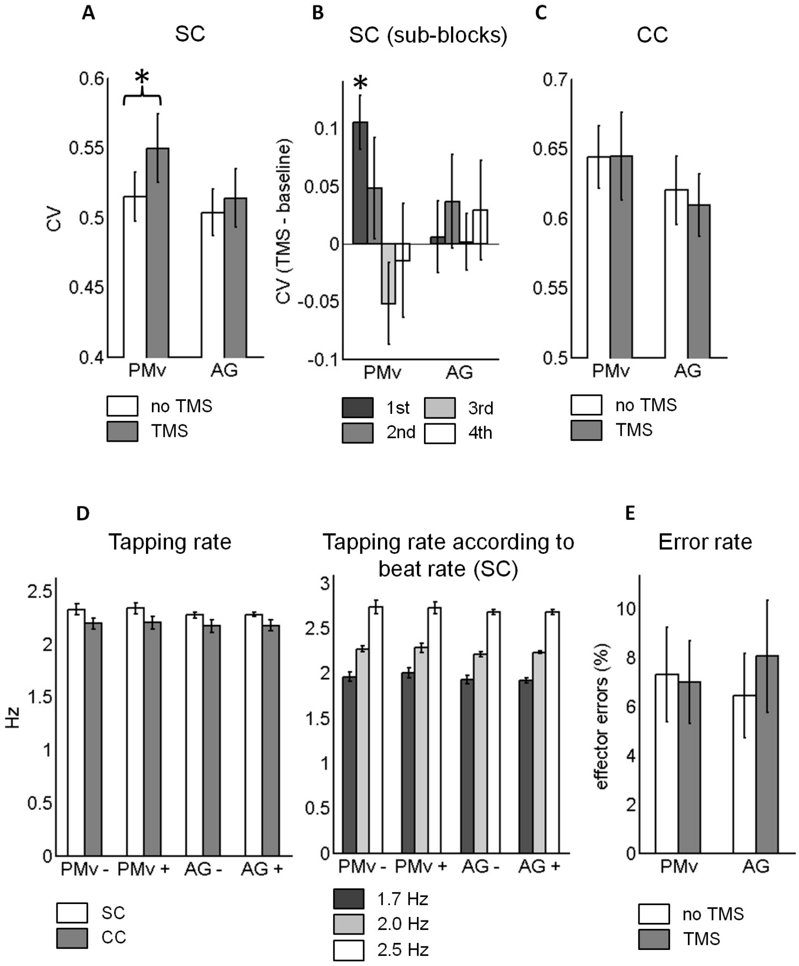


Figure 8.3.: *Behavioral effects of rTMS. A: Auditory-motor timing variability of tap-to-beat asynchrony in the synchronization condition (SC). B: Interaction of rTMS (no TMS/ TMS) and time (1st/ 2nd/ 3rd/ 4th sub-block) on CV in the SC. C: Control 1: Motor timing variability CV of tap-to-tap' asynchrony in the self-paced control condition (CC) where tap' is the predicted tap on the basis expected time according to the mean inter-tap-interval during the respective scrambled rhythm. D: Control 2: Tapping rate in the SC and CC (left side) and tapping rate in the according to beat rate of auditory rhythms in the SC (right side). "+" refers to the scan preceded by rTMS; "-" refers to the scan not preceded by rTMS. E: Control 3: Effector error rate.*

RATE (1.7/ 2.0/ 2.5 Hz) revealed no interaction of TMS and BEAT RATE in the PMv session (F(1.41,21.18) = 1.07, p = .36, Greenhouse-Geisser) or the AG session (F(1.64,24.61) = 0.41, p = .63, Greenhouse-Geisser). Only a main effect of BEAT RATE both in the PMv session (F(1.34,20.09) = 255.26, $p < .001$, Greenhouse-Geisser) and in the AG session (F(1.15,17.18) = 366.29, $p < .001$, Greenhouse-Geisser) could be observed (Fig. 8.3D, right side).

Control 3 - Effect on attention: Error rate

Any systematic effects of rTMS on attention in the SC condition could potentially influence the reported effect. The use of the non-cued hand, the effector error may indicate a decrease of attention to the task. However, a one-tailed paired samples t-test between the effector error rate in ”PMv no TMS” and ”PMv TMS” showed a trend towards significance in the opposite direction - a slightly decreased effector error rate during the ”PMv TMS” scan compared to ”PMv no TMS” scan (t(15) = 1.58, p = .07). There was no significant difference with regard to error rate between ”AG no TMS” and ”AG TMS” (t(15) = 0.381, p = .709), (Fig. 8.3E).

8.3.2. fMRI results

Synchronization Condition (SC) vs. Control Condition (CC)

As expected, a conjunction of SC vs. CC in all four independent scans yielded an activity increase in the dorsal auditory stream comprising bilateral Heschls gyrus (HG, BA 41/42), left posterior temporal gyrus (pSTG, BA 22) and left inferior ventral premotor cortex (PMv), as well as the posteriormost aspect of the pars opercularis (PMv, BA 6/44, Fig. 8.4). In addition, activity was enhanced in the right pars triangularis of the inferior frontal gyrus (IFG, BA 44/45), the right dorsal premotor cortex (PMd, BA 6), bilateral anterior insula (BA 13) and the cerebellar crus II (cf. Table 8.1 for Talairach coordinates).

Table 8.1.: *Activation foci in Experiment 3: Anatomical specification, hemisphere (R right, L left), Talairach coordinates (x, y, z), volume (mm3) and maximal Z scores (Z) of significant activations in the direct contrasts. HG: Heschl's gyrus; IFG: inferior frontal gyrus; IPL: inferior parietal lobe; PMd: dorsal premotor cortex; PMv: ventral premotor cortex; pSTG: posterior superior temporal gyrus; Z = z-score. *Based on the a priori hypothesis, activity increase in the right PMv after rTMS over the left PMv is reported on the basis of thresholded Z = 2.33 (p=.01), but uncorrected conjunction of the pairwise comparisons.*

Brain region	**Hemisphere**	**x**	**y**	**z**	**Z**
SC vs. CC: Conjunction of all scans					
PMv (BA 6/44)	L	-50	8	21	3.72
HG (BA 41)	L	-44	-13	3	6.52
HG (BA 41/42)	L	-53	-22	12	6.41
HG (BA 41)	R	43	-10	3	7.32
HG (BA 42)	R	61	-19	12	7.19
pSTG/IPL (BA 22/40)	L	-56	-34	21	6.83
PMd (BA 6)	R	46	2	48	4.26
IFG (44/45)	R	46	17	12	3.58
anterior insula (BA 13)	L	-38	17	9	3.29
anterior insula (BA 13)	R	28	23	9	3.95
Cerebellum. Crus II	L	-26	-70	-36	3.73
SC vs. CC: Conjunction of PMv TMS vs. all other scans					
PMv (BA 6)	R	58	2	18	3.21*
Cerebellum. vermal area V	R	1	-61	-6	3.29

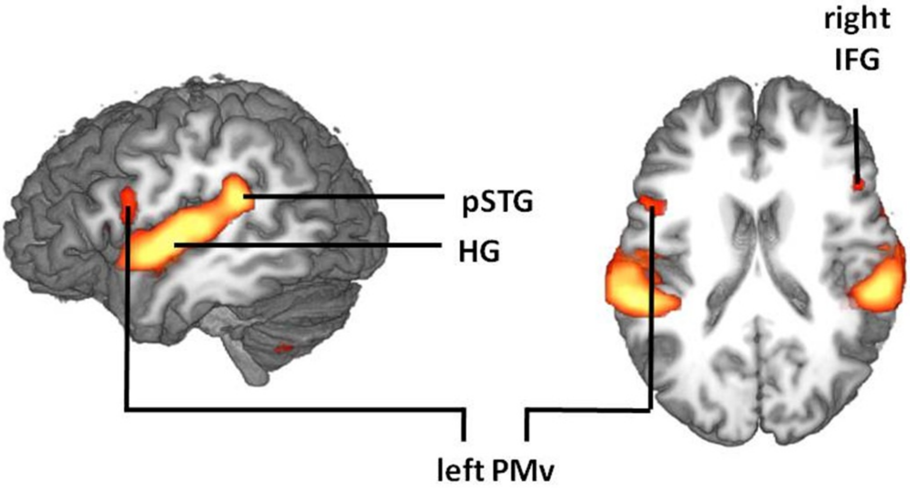


Figure 8.4.: *Synchronization (SC) versus self-paced control condition (CC). A conjunction of all four independent scans revealed activity increase in the bilateral Heschls gyrus, the left posterior superior temporal gyrus and the left PMv for auditory-motor timing (SC vs. CC); corrected at p<.005, displayed at p<.001 for illustration purposes).*

Activation increases after PMv TMS during SC vs. CC

A conjunction of the contrasts between ”PMv TMS” and all other scans for SC vs. CC allowed us to look for the effect of left PMv TMS on activity during auditory-motor integration. As hypothesized, rTMS over the left PMv stimulation was followed by a task-specific activation increase in the right inferior PMv. In addition, a significant activation increase was observed in the vermal area V of the anterior cerebellum (Fig. 8.5A).

The above stimulation-induced activity boosts in the right PMv and the anterior cerebellum revealed a differential role of these two areas in the preservation of synchronization accuracy. Linear stepwise multiple regression analyses with percent signal change for SC vs. CC during five-minute sub-blocks (1st, 2nd, 3rd, 4th) as predictors for the behavioral effect of left PMv stimulation were computed to test whether these changes are compensatory or unspecific effects of rTMS over the left

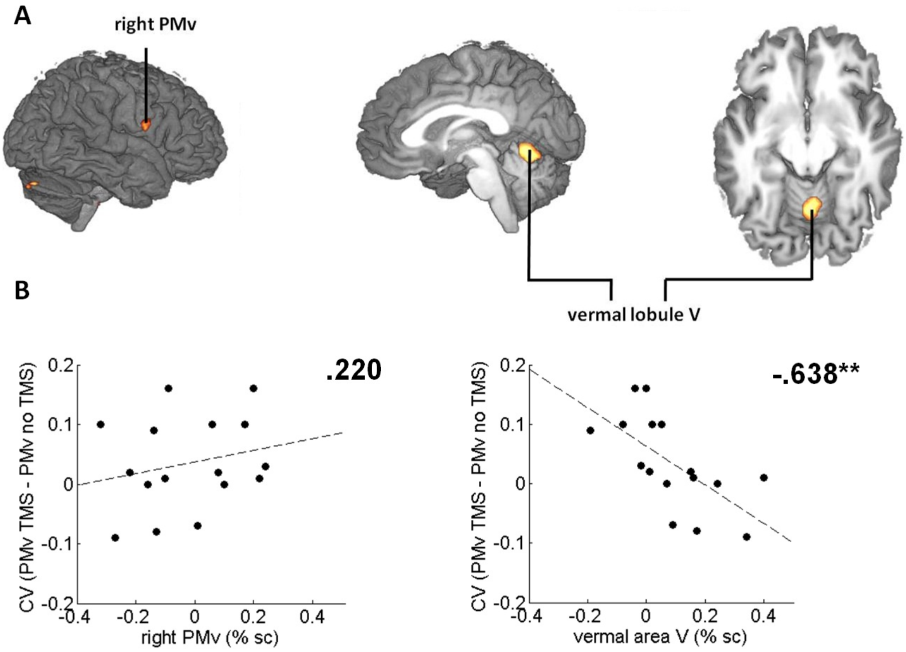


Figure 8.5.: *Compensatory activity following left PMv rTMS. A: rTMS over the left PMv triggered state-dependent activity increases (SC vs. CC, conjunction of rTMS PMv vs. no rTMS PMv, rTMS PMv vs. rTMS AG and rTMS PMv vs. no rTMS AG) in the right PMv (a priori hypothesis; uncorrected, displayed at p<.01) and the anterior midline cerebellum (corrected at p<.01). B: In contrast to right PMv activity (left side), the task-dependent cerebellar activity (right side) during the first five-minute sub-block following rTMS over the PMv predicted the preservation of auditory-motor synchronization accuracy. Subjects with higher activity increase in the vermal lobule V following rTMS over the PMv were more likely to retain synchronization accuracy.*

PMv. None of the four sub-blocks of right PMv activity significantly predicted the subjects behavioral performance. In contrast, the vermal area of the anterior cerebellum explained 40% variance of the behavioral effect of rTMS over the left PMv (multiple regression coefficient R = .638, $p < .001$): the higher the percent signal change in the first five minutes following TMS, the smaller was the effect of left PMv stimulation on synchronization accuracy (standardized regression coefficient beta = -.638; Fig. 8.5B). Thus, task-specific cerebellar activity in the first five minutes after rTMS predicted how much the subjects synchronization accuracy would be preserved in the ”PMv TMS” scan, indicating a compensatory mechanisms of this region in auditory-motor synchronization accuracy.

Notably, neither the right PMv nor the vermal area of the cerebellum predicted the behavioral changes of ”AG TMS” compared to baseline.

8.4. Discussion

Experiment 3 appears to be the first study to address compensatory short-term functional reorganization following interference with a region in the dorsal auditory stream in humans. The present combined rTMS-fMRI experiment probed the critical role of the left ventral premotor cortex (PMv) in auditory-motor timing, and investigated task-dependent activity increases that help to preserve auditory-motor synchronization following its disruption. Subjects synchronized left or right finger tapping to the beat rates (1.7, 2.0, 2.5 Hz) of auditory rhythms (synchronization condition; SC), and produced regular self-paced tapping during spectrally identical, but temporally scrambled versions of the same rhythms (control condition; CC). Results demonstrated that rTMS over the PMv, but not over a control region, disrupted auditory-motor timing, leaving motor timing variability, primary motor function and attention to task and stimuli intact. Moreover, it triggered task-dependent activity increases in the right PMv contralateral to the stimulation and the anterior midline cerebellum. In contrast to right PMv activity, cerebellar activity at the beginning of the scan predicted how much auditory-motor synchronization accuracy would be affected, with higher activity in less impaired subjects.

In the synchronization condition (SC), the beat rate of the auditory rhythms could change on a trial-to-trial basis. Accordingly, the task required the subjects to predict the onset of the upcoming isochronous beats on the basis of the first two beats of the respective rhythmic stimulus and align their finger tapping to the predicted onsets accordingly. Accurate auditory-motor timing requires resources that enable precise feed-forward prediction of ex-afferent auditory and re-afferent somatosensory and proprioceptive feedback. This feed-forward interpretation is in line with the assumption that the perception of beats and the generation of taps rely on a shared central timeline (Aschersleben & Prinz, 1995). Importantly, while tap-to-beat asynchrony was affected, self-paced tapping remained intact. This suggests that specifically the variability of auditory-motor timing, but not that of motor timing was impaired after rTMS over the PMv. Moreover, these results could not be explained by a degradation of motor output, or overall auditory-motor coupling, since the subjects adjusted their tapping rate to the respective beat rate independent of the rTMS condition. Finally, results show no impairment of the subjects attention to the task, since rTMS had no effect on the effector error rate.

The present behavioral results suggest that the left inferior PMv is part of a network critically involved in auditory-motor timing, i.e. left and right hand tapping to an auditory beat of musical rhythms. This result in line with the present fMRI findings (cf. Fig. 8.4), as well as with previous imaging studies reporting this region within the context of auditory-motor synchronization (e.g Rao et al. (1997); Jancke et al. (2000); Thaut (2003)). However, while other regions have been reported to be critically involved in right hand tapping synchronization such as the lateral cerebellum and left dorsal premotor cortex (Olmo et al., 2007), the present study is the first to demonstrate an effector-independent impairment of auditory-motor timing. This result is consistent with the framework proposing that rhythmic prediction is effector-independent and sub-served by an audiomotor fraction of a full-blown action representation (Schubotz, 2007).

Note that Malcolm et al. (2008) did not find a significant effect of rTMS over the left PMv on auditory-motor synchronization. This might be partly explained by different measures of synchronization, such as absolute tap-to-beat asynchrony in the above study (Malcolm et al., 2008) and synchronization accuracy in the present study. Moreover, in contrast to the former, the beats used here were surrounded by other rhythmic events (Fig. 8.1), as it is the case in music. Compared to metronome clicks, they require more attentional resources to be directed to the auditory modality.

The variability of tap-to-beat synchronization was impaired after repetitive TMS interference with a region of the left dorsal auditory stream, which is frequently regarded as tuned to language functions. In all four independent fMRI-scans, the SC versus the CC yielded activity in regions of the dorsal-auditory stream the bilateral Heschls gyrus, the posterior superior temporal gyrus (pSTG) and the PMv. Remarkably, the pSTG and the PMv were left-lateralized. Comparable activity increases are considered to be related to speech perception and production (Hickok & Poeppel, 2007; Rauschecker & Scott, 2009). However, like speech, a non-speech task such as synchronization of finger tapping to an auditory beat requires a temporally precise prediction of auditory, somatosensory and motor information. The enhanced recruitment of bilateral primary auditory, left temporo-parietal and premotor regions reveals that synchronization of left and right finger tapping to a musical beat exploits a circuit that is otherwise involved in vocalization and speech. Note that this pattern of activity is unlikely to be caused by increased sub-vocalization during the synchronization condition. There was no consistent activity increase in areas characteristic for motor imagery and motor preparation such as the primary motor cortex, primary and secondary somatosensory areas, and in particular the SMA/pre-SMA, an area which has been shown to be most reliably involved in vocal imagery (Kawashima et al., 2000; Riecker et al., 2000; Thobois et al., 2000; Kleber et al., 2007).

As hypothesized, activity in the homologue right PMv (contralateral to the stimulated site) was enhanced for auditory-motor timing following rTMS over the left PMv in comparison to all other scans. This result is in line with evidence provided by both stroke and rTMS studies, which demonstrated task-dependent activity increase in non-dominant homologue regions contralateral to the affected primary motor, premotor or prefrontal sites during motor, visuo-motor and speech tasks (O'Shea et al., 2007; Nowak et al., 2008; Kell et al., 2009). Such activity boosts are hypothesized to arise from decreased transcallosal inhibition that occurs as a result of the disruption of the respective area in the left or the right hemispheres: Although callosal fibers are predominantly excitatory (Innocenti, 1986; Bloom & Hynd, 2005), transcallosal inhibition is thought to be mediated by these excitatory fibers projecting onto GABA-ergic inhibitory neurons (Ferbert et al., 1992).

Despite the occurrence of the hypothesized task-specific increase in the right PMv after left PMv stimulation, our assumption concerning the compensatory nature of this activity was not supported. None of the four five-minute sub-blocks of the scan following left PMv stimulation significantly explained the effect of the latter on the subjects auditory-motor synchronization. This result lends support to studies demonstrating no compensatory or even adverse behavioral effects of activity increase in the non-dominant hemisphere contralateral to the affected region (Liepert et al., 2007; Grefkes et al., 2008; Nowak et al., 2008; Kell et al., 2009). The functional relevance of the enhanced recruitment of contralesional primary motor and premotor cortex is, however, still under debate (Murase et al., 2004; Stinear et al., 2007; Nowak et al., 2008).

Besides the right PMv, an extended region in the midline anterior cerebellar lobe (vermal lobule V) was more strongly activated during SC when preceded by rTMS over the left PMv compared to all other scans. Importantly, in contrast to the right PMv, activity in the initial five minutes after rTMS in the anterior cerebellar lobe reliably predicted how well subjects preserved auditory-motor synchronization accuracy during the scan following left PMv stimulation. This covariance was specific to TMS over the left PMv and not present following TMS over the left AG (control site). Unlike the right PMv which is interconnected with the left PMv via transcallosal fibers, the vermal lobule V is not known to have pronounced multi-synaptic projections to the left PMv. Kelly & Strick (2003) induced retrograde tracers into the adjacent frontal motor site arm area of the primary motor cortex and found only few labeled Purkinje cells in the vermal lobules IV-VI, with most clusters beginning 4 mm from the midline. Moreover, in contrast to the cerebellar hemispheres, which project to the dentate nucleus that shows distinct output to the PMv (Strick et al., 2009), the vermal lobule projects to the fastigial nucleus (Habas et al., 2009). Notably, the output of the midline cerebellum, the fastigial nucleus, has been proposed to serve as an interface between cerebro-cerebellar and spino-cerebellar loops, i.e. as a comparator between top-down motor commands and bottom-up visual, vestibular, proprioceptive and exteroceptive feedback signals which provide information on the current state of the system (Mori et al., 2004). Support for the role of the anterior vermal lobe in the temporal integration of multimodal information is provided by neuroimaging: While generally sensorimotor in contrast to cognitive tasks are known to activate the anterior part of the cerebellum (Stoodley & Schmahmann, 2009), the anterior vermal region has been proposed in temporal processing of multisensory, e.g. tactile and proprioceptive, information (Kavounoudias et al., 2008).

Consistent with the current motor timing task, Spencer et al. (2007) demonstrated a recruitment of this area in discrete in contrast to continuous timing, which contains a pause inserted before each flexion phase, such as rhythmic finger tapping in the current experiment. In line with the current data revealing an inverse relationship of anterior vermal lobe activity and the impairment of tap-to-beat asynchrony, this area has been recently associated with reduced reaction time (RT) variability (RT coefficient of variation) in children (Simmonds et al., 2007). Finally, this region has also been reported during reduced predictability of visual (Toma et al., 2003) and somatosensory (Tesche & Karhu, 2000) sequences, increased difficulty of temporal auditory tasks, as well as perception and production of complex versus isochronous visual rhythms (Xu et al., 2006).

Taken together, the short-term task-dependent compensatory activation of the vermal area V suggests that more resources were devoted to temporal mismatch detection between bottom-up (auditory and somatosensory input) and top-down (corollary discharges of motor output) information after interference with the left PMv. This activity increase occurred only following the disruption of the PMv, which is a causal node in auditory-motor information timing, but not the control region, which underlines the causal involvement of the left PMv in auditory-motor timing. In subjects with a more pronounced activity increase in the vermal area V following PMv stimulation, the deteriorating effect of PMv stimulation on synchronization accuracy was mitigated.

It cannot be deduced from the present findings whether the enhanced temporal mismatch detection between these information channels may have occurred due to altered (i) top-down, via remote influence of rTMS over the left PMv, (ii) bottom-up, via the behavioral impairment following left PMv stimulation or (iii) interaction of top-down and bottom-up information. Furthermore, to probe whether the compensatory metabolic activity in the anterior midline cerebellum reflects a more general, supramodal mechanism of temporal mismatch detection, future studies should test whether it is bound to auditory cues or occurs during synchronization to visual and somatosensory cues, as well.

In conclusion, *Experiment 3* suggests that the left PMv critically contributes to effector-independent auditory-motor timing. Repetitive TMS interference with its activity triggers differential compensatory mechanisms in remote sites: While task-specific activity increase in the right PMv contralateral to the stimulation region does not help to retain behavior, activity in the anterior cerebellum can be linked to a transiently effective compensation of auditory-motor timing after PMv disruption.

Part III.

General discussion

When people listen to music, they frequently feel an urge to entrain their body movements to its regular beat by head nodding, toe or finger tapping and dancing. Indeed, there is a tight link between movement in music, since the beat rate range of different popular musical styles peaks around 2 Hz closely matching the rate of repetitive movements (Moelants, 2003; van Noorden & Moelants, 1999). Although auditory-motor coupling to music has been proposed to be a cross-cultural human universal (Nettl, 2000), it was unknown which brain mechanisms give rise to this auditory-motor integration behavior. The goal of the experiments conducted in the present thesis was to explore the neural basis that leads to auditory-motor coupling to a regular pulse in musical rhythms, i.e. to auditory-motor integration of a musical beat rate.

Specifically, the current thesis focused on the contribution of a motor-related cortical region classically conceived as involved in vocalization and speech processes - the inferior part of the ventral premotor cortex (PMv) extending into BA 44 (Broca's area on the left side). A short summary of the results obtained in the current experiments is presented below, followed by a comparative discussion of the results, as well as by a section on limitations of the current findings and their implications for future research.

9. Summary of obtained results

Using functional magnetic resonance imaging (fMRI), *Experiment 1* aimed at probing the involvement of motor-related brain regions when subjects attention is directed to rhythms they individually prefer compared to those that they do not. Specifically, the experiment was designed to test whether aesthetic appreciation of rhythms with individually preferred beat rate (tempo) around 2 Hz will be accompanied by activity increase in the PMv which has been previously shown to be involved in rhythm perception tasks (*H1*). To test whether the hypothesized activity can be explained by increased internal auditory-motor simulation of the auditory beat rate, activity during preferred rhythms was compared by activity increase during a perceptual rhythm task - the beat rate judgment task (*H2*). In line with the notion of sensorimotor-driven forward models and the evidence for the involvement of motor-related areas in perceptual rhythm tasks, we assumed that the tempo judgment task required enhanced sensorimotor simulation. The obtained results revealed beat rate to be the most important temporal property of the musical rhythm with regard to the subject's aesthetic judgment. Importantly, musical rhythms with preferred tempo but not with preferred timbre, a non-rhythmic property of the musical rhythms, engaged the left PMv confirming hypothesis *H1*. Moreover, the PMv activity increased to the same extend as during the perceptual rhythm task, lending support to the second assumption (*H2*). The activity boost in the left PMv was unlikely to be explained by subjects humming along with the rhythm or by vocal imagery, since no significant activity increase was found in the supplementary motor area (SMA) or primary motor cortex. Importantly, the increase in PMv activity covaried linearly with how strongly the subjects preferred a certain beat rate.

Despite this evidence, it remained uncertain whether an interference with activity in the left PMv would affect tempo preference strength. In *Experiment 2*, offline repetitive Transcranial Magnetic Stimulation (rTMS) was used in a similar experimental paradigm to probe the *causal* contribution of the left PMv to auditory beat rate preference. Individual tempo preference strength and stability within and across sessions was hypothesized to be temporarily disrupted following rTMS interference with the left PMv (*H3*). Moreover, it was assumed that the latter effect would covary with the effect of PMv stimulation on the perceptual rhythm task (*H4*). As predicted (*H3*), rTMS over the left PMv temporarily interfered with individual tempo preference strength depending on the individual strength of tempo preference in the control session. Moreover, PMv stimulation temporarily disrupted the stability of individual tempo preference strength within and across sessions. These effects were specific to the preference for tempo in contrast to the preference for timbre and bound to the first half of the experiment following PMv stimulation. However, the hypothesis *H4* was not confirmed by the results, since the disruption of beat rate preference strength could not be explained by an impairment of beat rate recognition.

While *Experiments 1* and *2* revealed that a motor-related region - the left PMv - modulates auditory preference for a beat rate, it remained unclear whether the same cortical region is also causally involved during coupling of movement to an auditory beat. If this were the case, perceptual preference for a beat rate exploit the same auditory-motor integration resources as auditory-motor synchronization. Furthermore, an additional aim was to identify mechanisms that help to preserve auditory-motor timing, in particular, the compensatory role of the right PMv, contralateral to the stimulation. Accordingly, *Experiment 3* used the combination of offline rTMS and fMRI to determine the causal contribution of PMv to auditory-motor synchronization (*H5*) and identify task-dependent compensatory mechanisms that help to preserve task performance following its disruption (*H6-H7*). As expected, activity in the dorsal auditory stream - including Heschl's gyrus, posterior superior temporal gyrus and the PMv (BA6, extending into BA44) - was enhanced for the synchronization compared to the control condition in all scans. Moreover, left PMv impaired auditory-motor synchronization according to *H5*, an effect that wore off with time after the end of stimulation. Although activity increased in the unaffected contralateral right PMv after left PMv stimulation confirming *H6*, it yet did not predict the behavioral effect of rTMS across subjects. Thus, for the right PMv *H7* was not supported. However, the subjects' performance after left PMv could be predicted from task-specific activity in the anterior midline cerebellar region according to *H7*, an area previously associated with reduced response variability and discrete motor timing. In conclusion, the above results suggest that the left PMv is causally relevant for auditory-motor integration. While activity increase in the ventral premotor region contralateral to the stimulation region did not help to preserve behavior, the anterior cerebellum could be linked to a compensation of auditory-motor synchronization after PMv disruption.

10. Comparison across experiments and implications of obtained findings

A conjunction between the functional imaging results of *Experiments 1* and *3* revealed a partial overlap of neural mechanisms between effects of auditory beat rate preference and auditory-motor coupling to the beat rate of the musical rhythms (Fig. 10.1). The two sites of overlap were both located in the left PMv, ventral to the inferior frontal sulcus and caudal to Broca's area. One was situated in the anterior and superior region just below the inferior frontal sulcus and extended into the precentral sulcus; the other was located more inferiorly and was adjacent to the opercular region. These regions of overlap most probably correspond to areas *6v1* and *6r1* of the subdivision recently proposed by Amunts et al. (2010) on the basis of cyto- and receptoarchitectonic features (cf. Fig. 3.1). According to the hierarchical cluster analysis revealing similarity/distance based on receptor density distribution of six receptors, areas *6v1* and *6r1* appeared in one cluster, separated from areas op8, op9, BA 44 and 45 (Amunts et al., 2010). Since regions with similar receptor distributions tend to show similar functions (Zilles & Amunts, 2009), this finding suggests that the two regions of overlap are anatomically and functionally homogeneous and will be subsequently discussed together.

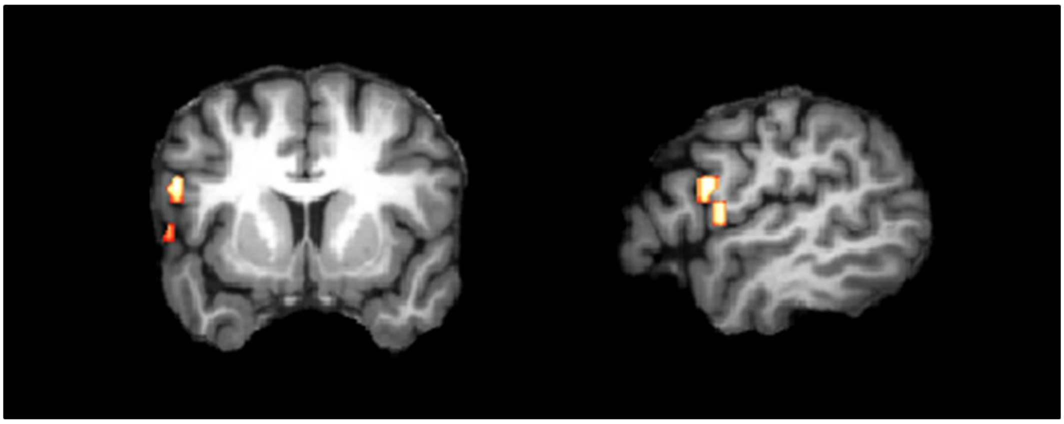


Figure 10.1.: *Conjunction between imaging results in Experiments 1 and 3. The only overlap between BOLD activity increase for auditory beat rate preference and synchronization to an auditory beat rate was found in the left PMv.*

Since the region of overlap extended into the precentral sulcus, it can be said that it was partly located at the transitional area from agranular premotor cortex to dysgranular pars opercularis (Broca's area) of the inferior frontal gyrus. It has been proposed that the function of Broca's area in speech production, comprehension and syntactical analysis may have its evolutionary origins in the premotor cortex (Fazio et al., 2009). The current findings show that auditory-motor integration of rhythm critically depends on left premotor areas extending into Broca's region.

Indeed, the timing of events over prolonged periods of time are crucial in production and comprehension of both speech and music. However, as already mentioned in Chapter 1, unlike speech, music typically consists of repetitive, and thus more predictable, temporal patterns. In the present work, one of the most prominent types of repetitive rhythmic patterns in music was investigated - an isochronous beat. Structurally, it is the simplest type of rhythm, since (i) event cues marking a beat are recurring periodically, i.e. the interval length between events remains constant within a rhythmical trial and (ii) a recurring beat cue does possess the lowest ordinal complexity[1]. However, unlike most studies employing isochonous rhythms,

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[1] In the current experiments, each rhythmic cue, including the beat, could be marked by two differ-

the cue for beat rate was not presented in isolation, but embedded into additional isochronous and non-isochronous cues, e.g. those marking beat grouping or beat subdivision. Moreover, all experiments employed an event-related trial design, in which subjects were typically exposed to beat rates that could change on a trial-by-trial basis, so that new predictions concerning the onset of the beats had to be made at the beginning of each trial.

It is remarkable that auditory-motor integration of rhythm revealed a left-lateralized component that is classically associated with speech-related processing. However, the left lateralization might also be related to sequence complexity and sequence storage load, rather than to overlap with speech-related neural resources. In contrast to the left, the right premotor cortex is involved in advanced stages of sequence learning and modulated by sequence complexity, as well as length in motor (Sadato et al., 1996) and perceptual sequences (Schubotz & von Cramon, 2002a). Thus, it is not surprising that auditory-motor integration of an isochonous periodic pulse rate, the most elementary rhythmic parameter, draws on a left-lateralized premotor component.

The results obtained in *Experiments 1* and *2* suggest that the left PMv is causally relevant for perceptual preference of auditory beat rate. Functional MRI results revealed that in the aesthetic judgment task, PMv activity was not elevated, unless subjects were presented with rhythms which beat rate they subjectively preferred. The aesthetic judgment task did not require auditory-motor integration of the beat rate. Indeed, judgment analysis revealed that, overall, a non-timing related factor - timbre - was the most important factor determining their aesthetic judgments.

The present findings advocate the notion that more neural resources in the motor

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ent sounds. The sequence of these sounds differed according to the beat grouping/meter, e.g. 3 beats (ABA-ABA), 4 beats (ABAB-ABAB) and 5 beats (ABAAB-ABAAB). Nevertheless, the sequential structure determined by the metre was counterbalanced across different beat rates, i.e. it is unlikely, it had an influence on the perception of or on the synchronization to the beat.

system may be tuned to preferred in contrast to not preferred beat rates. This is in accordance with results suggesting that the PMv activity is modulated by previous auditory-motor coupling experience (Lahav et al., 2007; Bangert et al., 2006; Baumann et al., 2007). The latter effect has also been reported with regard to the influence of visuo-motor coupling on PMd (Calvo-Merino et al., 2005, 2006) and PMv activity (Cross et al., 2006). Although the term ”action resonance” (Cross et al., 2006) has been used to describe premotor activation during action observation, it might be misleading when applied to the present findings. Firstly, *Experiment 2* suggests that activity in the PMv does not only accompany, but causally contribute to perceptual preference of auditory rhythms; secondly, the activation of this motor-related site does not necessarily entail a full re-enactment (Schubotz, 2007). Therefore, it may not be the most parsimonious interpretation.

Although the present experiments revealed overlapping PMv contribution to perceptual and motor tasks, such evidence does not suggest the conclusion that the ”mirror” or more specifically, the ”echo” neuron system may contribute to rhythmic preferences on the basis of fMRI and rTMS results alone. The PMv in monkeys contains a variety of neurons besides these type of neurons[2] and there has been so far no direct evidence for mirror neurons in the human PMv.

How do these findings fit into the framework of internal simulation outlined in the introductory chapters? Figures 10.2 and 10.3 propose neural mechanisms of rhythm prediction (and based on this of perceptual rhythmic preference) and auditory-motor synchronization on the basis of internal forward models. The proposal draws on the present results, as well as on previous findings related to sensorimotor integration and motor cognition. Thus, this account attempts to incorporate the PMv contribution into a broader functional network enabling internal feed-forward prediction of

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[2] Kohler et al. (2002) report only 13% of neurons in area F5 in monkeys to possess ”echo” properties.

auditory rhythm.

Figure 10.2 is a schematic diagram of possible neural mechanisms enabling rhythm prediction, which perceptual rhythmic preference may draw on. It is partly consistent with the model of Schubotz (2007), however, it also considers cerebellar contribution and proposes neural implementation of the comparator module. When the beat rate of the rhythm is not known, the motor system starts to interpolate the onset of the beat from the relative intensity or pitch modulations in the incoming auditory signal. The SMA sends an efferent signal to the body directly or via the primary motor cortex, that is suppressed[3], because it is used to predict the beat onset, but not to synchronize body movements to the beat on top of sensory prediction. At the same time, an efference copy of this command is send to the PMv and possibly to the lateral anterior cerebellum (aCB) which together have been suggested to form a closed cortico-cerebellar circuit (Strick et al., 2009).[4] This circuit emulates the predicted sound onset of the upcoming beat. The predicted sound onset is send to auditory areas in the dorsal auditory stream such as posterior superior temporal cortex (pSTG) and possibly to the midline aCB (vermal area V), that receive auditory information on the actual sound onset via the primary auditory cortex (Heschl's gyrus; HG).

Why could the latter two regions potentially serve as a comparator module in auditory-motor integration? The pSTG is proposed based on evidence demonstrating an attenuation of activity in sensory areas by a corollary discharge from the motor system during self-induced movement (Sperry, 1950; von Holst & Mittelstaedt, 1950), such as from the motor to the auditory systems in humans (Paus et al., 1996) and insect models (Poulet & Hedwig, 2006), as well as from the mo-

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[3] In the present model, it is left open, at what stage the efferent signal is suppressed. It is possible that this happens at the cortical level and the signal does not reach the M1 as suggested by Schubotz (2007).

[4] Cf. Ramnani (2006) for the role of cerebellum in forwards models in cognitive control.

tor to the tactile (Blakemore et al., 2000, 1998; Christensen et al., 2007) and from the motor to the visual systems (Wurtz, 2008). The midline aCB draws on findings suggesting that its output, the fastigial nucleus, serves as an interface between cerebro-cerebellar and spino-cerebellar loops and has access to both top-down motor commands and bottom-up visual, vestibular, proprioceptive and exteroceptive feedback signals (Mori et al., 2004).

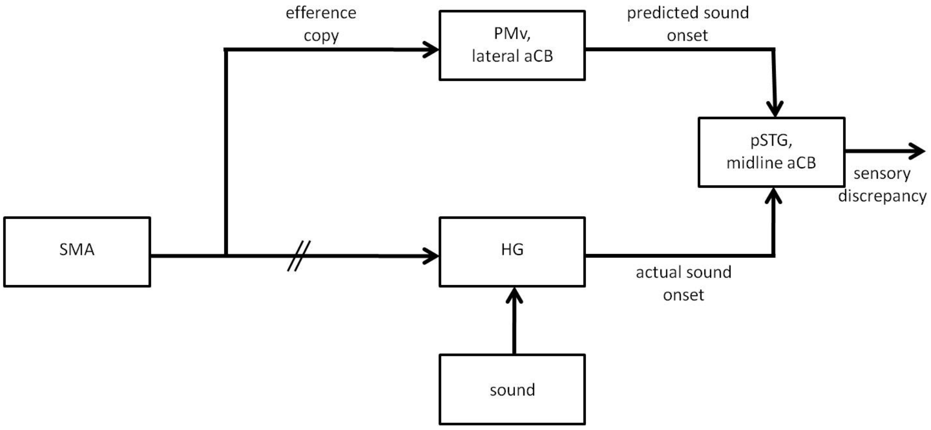

Figure 10.2.: *Proposed anatomical basis of auditory rhythm prediction*

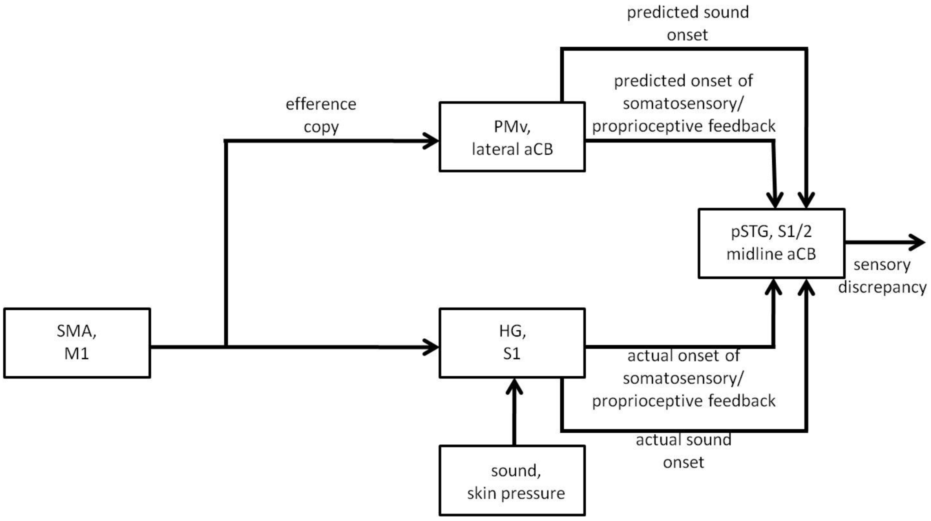

Figure 10.3.: *Proposed anatomical basis of auditory-motor synchronization*

Figure 10.3 is a schematic diagram of the anatomical basis of a forward model serving auditory motor synchronization by finger tapping. It incorporates the forward model for the prediction of auditory beat onset; however, on top of this, it predicts the onset of somatosensory and proprioceptive feedback on the basis of an efference copy of the efferent signal sent from the SMA and M1 via the corticospinal tract to the body to perform a movement such as index finger flexion for finger tapping. Moreover, it compares the actual onset of this movement-induced proprioceptive and somatosensory feedback with the predicted onset, most probably in the somatosensory cortices (S1/S2) in addition to the midline aCB. Again, the latter is based on studies reporting attenuating sensory signals due to a corollary discharge from motor to sensory systems as referred to above. In line with this notion, *Experiment 3* revealed increased activity in the left somatosensory cortex, specifically its finger representation, following PMv stimulation (Fig. A.4).[5] This observation supports the current model, since interference with the PMv may have disturbed the forward models and consequently distorted accurate prediction of the onset of proprioceptive and somatosensory feedback preventing sensory attenuation. Besides the reported midline aCB activity, somatosensory activity may reflect the sensory discrepancy arising from the mismatch of actual and predicted timing.

The output of the midline aCB, the fastigial nucleus, has been proposed to serve as an interface between cerebro-cerebellar and spino-cerebellar loops (Mori et al., 2004) and the midline aCB has been shown to be associated with the temporal integration of multimodal (extrinsic and intrinsic) information (Kavounoudias et al., 2008). Accordingly, it may serve as a comparator across (and not just within) modalities on a common central timeline (Fraisse, 1980; Aschersleben & Prinz, 1995, 1997) by relating the actual onset arriving from bottom-up exafferent (auditory) with reafferent (proprioceptive, somatosensory) feedback signals, as well as with the predicted onset generated by the top-down efferent signals.

Can auditory-motor integration of rhythm reach an intermediate level with regard to its motor and sensory component? It is conceivable that a stronger involvement

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[5] This effect did not reach significance being slightly below the applied statistical threshold.

of the motor system during auditory rhythm perception may trigger forward models in the PMv that predict somatosensory and proprioceptive in addition to auditory input, perhaps because these forward models exploit interconnected networks. In this case, the discrepancy between predicted and actual somatosensory input may ultimately lead to an adjustment of the motor command. In other words, *a stronger involvement of the PMv may induce enhanced somatosensory prediction and, consequently, the urge to alleviate the sensory mismatch between actual and predicted input by tuning-in to the beat by body movement or vocalization.*

Note that the above model of auditory-motor synchronization of rhythm accounts for finger tapping based on the present experiments. It does not incorporate the vestibular component that is present when whole body or head movements are synchronized to an auditory rhythm. However, it is likely that the prediction of vestibular input could be incorporated in the current model as an additional informational stream due to its connections to both the PMv (Lobel et al., 1998) and the medial aCB (Mori et al., 2004).

11. Limitations and future research directions

The present results shed light on the neurofunctional basis of auditory-motor integration of rhythm. However, they do not elucidate how rhythmic preferences are acquired. Moreover, they do not show how these preferences are engraved in the central nervous system, since the current methods and experimental paradigms did not address changes on a macro- or micro-anatomical scale. Previous findings suggested that a stimulation of the vestibular system by body and, in particular, head movement can be effective in priming auditory rhythmic preferences in infants and adults (Phillips-Silver & Trainor, 2005, 2007, 2008). From a developmental perspective, it would be interesting to address the influence of maternal preferred walking speed during the prenatal stage on the infants' rhythmic preferences. Moreover, research across different primate species could reveal, whether auditory-motor coupling to rhythm is innate or rather determined by exposure to auditory-motor and auditory-vestibular coupling, e.g. when subjects are bounced to rhythms.

How may these rhythmic preferences be manifested neurophysiologically? Since the PMv is innervated by projections from the auditory association areas via the arcuate fasciculus and sends cortico-fugal projections to the vestibular nuclei (Akbarian et al., 1993, 1994), it is conceivable that exposure to particular rhythms through walking, speech etc. may modulate the contribution of the PMv to particular auditory rhythms. In terms of the forward model approach, the selection (weighting) of forward models in the PMv by auditory input may be implemented in terms of comparator output from sensory, in this case auditory areas. In a loop with the lateral cerebellum, the PMv may provide more accurate predictions for these familiar rhythms.

Unlike PMv, auditory areas did not show an activity increase when subjects listened to rhythms with individually preferred versus not preferred beat rate (Fig. A.3). However, percent signal change analysis did not reveal the reversed pattern that may be expected from the current model, i.e. an attenuation of the signal in left primary auditory and auditory association areas during preferred as compared to not preferred rhythms due to a more accurate forward prediction for preferred rhythms.[1] To further test this assumption, it would be necessary to repeat *Experiment 2*, but complement it with a subsequent fMRI measurement. If the above assumption is correct, interference with PMv would not only disrupt rhythmic preferences, but also increase activity in auditory sites due to a mitigated attenuation of sensory input by the PMv related to increased mismatch between predicted and actual auditory timing.

Despite the overlap in activity increase for both preferred auditory beat rate and auditory-motor synchronization to the beat rate, as well as the application of the forward model both to perceptual and motor integration of rhythm, the behavioral link between rhythm prediction and preference has not been provided yet. It would be important to demonstrate that subjects show a better performance when predicting individually preferred compared to not preferred auditory beat rates.

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[1] Unlike the findings with regard to the PMv, there was no significant covariation of beat rate strength and attenuation of activity in primary auditory and auditory association areas (Fig. A.3). Note, however, that the difference in temporal mismatch between real and expected beat onset of individually preferred and not preferred beat rates around 2 Hz may be too subtle to be reflected by the BOLD signal of primary and secondary auditory cortex.

Experiments 1 and *2* showed conflicting results with regard to the beat rate recognition task. Despite the fact that left PMv activity increased during this task as much as during preferred rhythm in the aesthetic judgment task, the effect of inhibitory PMv stimulation on beat rate preference could not be explained by its effect on beat rate recognition. It is conceivable that this explicit beat rate task may have drawn on compensatory sensorimotor resources, since a simulation of the beat rate was required to achieve the task in contrast to the aesthetic judgment task. As in *Experiment 3*, subsequent fMRI may shed light on potential compensatory resources.

rTMS interference with the left PMv produced a five to ten minutes long disruption of both beat rate preference and accuracy of auditory-motor synchronization. These disruptive effects were mitigated not later then ten minutes following rTMS. However, it remains unclear - in rTMS research in general - whether the behavioral and neural effect of rTMS drops linearly or rather according to non-linear dynamics. Moreover, it should be addressed, how the reported behavioral effect of rTMS co-varies with compensatory activity in the cerebellum. A concurrent combination of rTMS and fMRI may shed light on the trial-by-trial modulations of performance and cerebellar activity induced by PMv stimulation.

Finally, it remains unclear whether the compensatory metabolic activity in the anterior midline cerebellum reflects a more general, supramodal mechanism of temporal mismatch detection, or whether it is rather bound to the auditory modality. To probe this, future studies should implement *Experiment 3* or similar paradigms in different modalities, i.e. by including tasks that require synchronization to visual or tactile cues.

Part IV.

Appendix

A. Figures

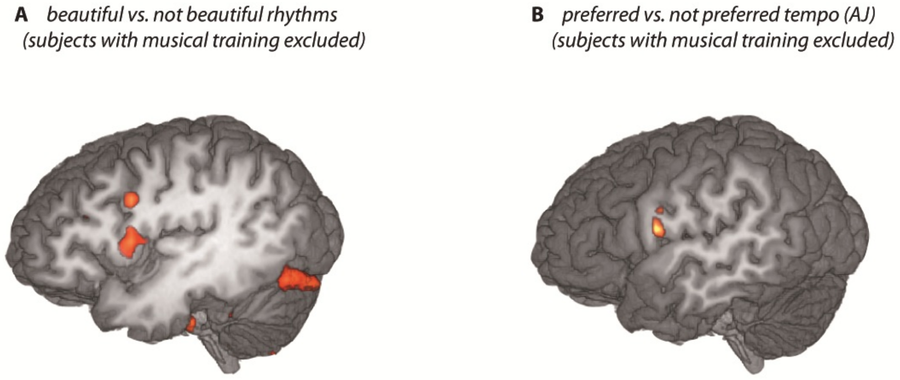

Figure A.1.: *Experiment 1: Effects of rhythmical preference on subjects without musical training. Contrasts beautiful vs. not beautiful rhythms (A) and preferred vs. not preferred tempo (B) (p=.01, uncorrected) when excluding six and five subjects, respectively, who received instrumental training or attended a choir.*

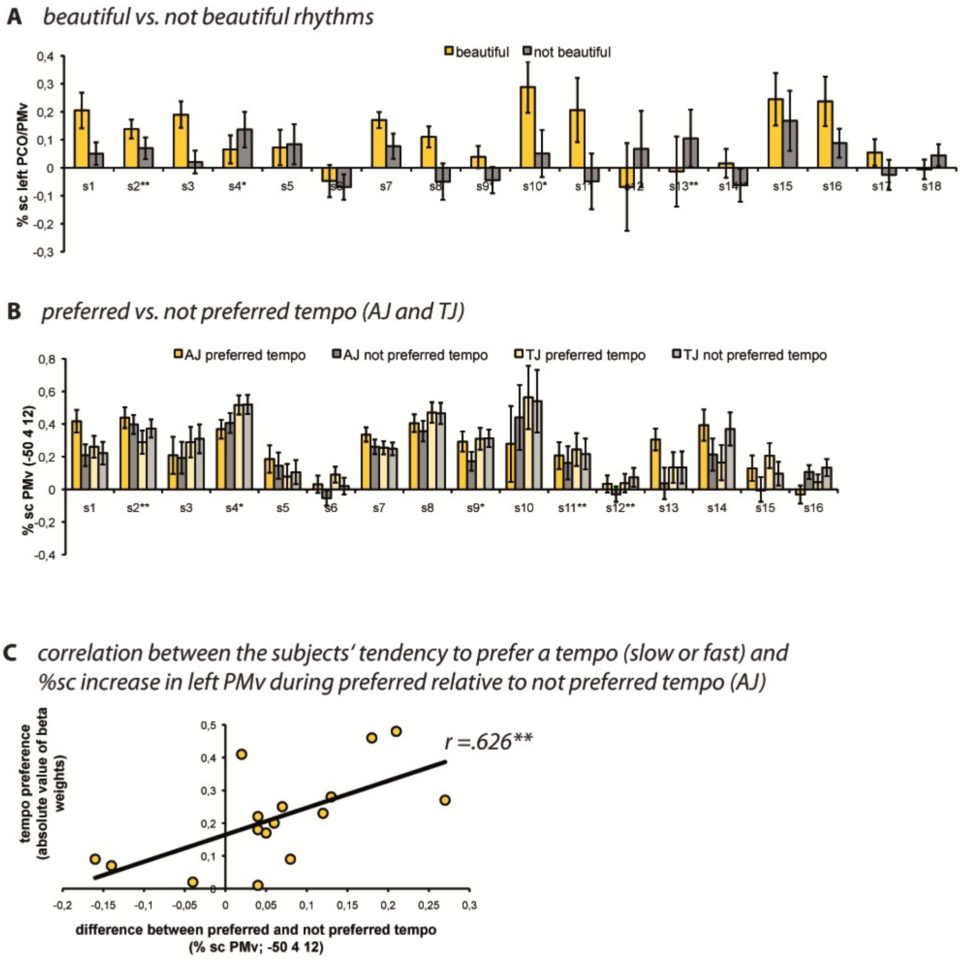

Figure A.2.: *Exp. 1: Effects of rhythmical preference on individual percent signal change in ventral premotor ROIs. Subjects marked with * received instrumental training or attended a choir at some point in their life, but did not report any musical activities at the time of their participation in the experiment; subjects marked with ** reported musical activities for 4 to 5 hours per week at the time of their participation in the experiment. A. % sc of each subject in left PCO/PMv ROI during rhythms judged as beautiful and not beautiful. B. % sc in PMv during rhythms with preferred and not preferred tempo in both the aesthetic judgment (AJ) and the tempo judgment (TJ) conditions. C. Correlation between the strength of tempo preference (slow or fast tempo) and the % sc increase in PMv during preferred relative to not preferred tempo (AJ).*

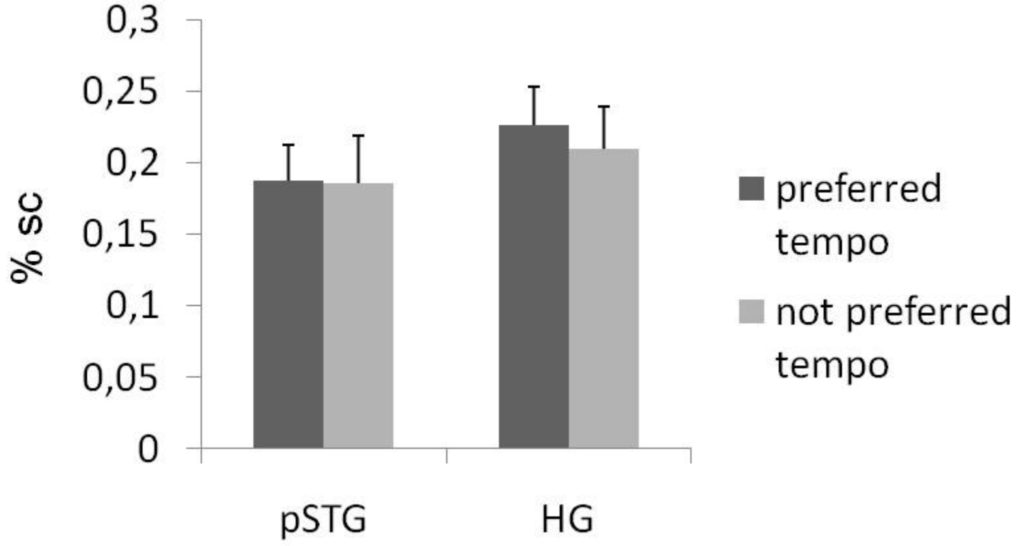

Figure A.3.: *Experiment 1: Activity in auditory areas during rhythms with preferred and not preferred tempo (beat rate). No percent signal change difference was revealed in the left Heschl's gyrus (HG; Talairach coordinates: -44 -13 3; t = .789, p = .47, one-tailed) or the left posterior superior temporal gyrus (pSTG; Talairach coordinates: -56 -34 21; t = .088, p = .22, one-tailed). Note that the activity increase in auditory areas for preferred versus not preferred tempo did not show an inverse correlation with the individual strength of tempo preference in either of the sites (pSTG: r = -.278, p = .15, one-tailed; HG: r = .154, p = .29, one-tailed). The above coordinates were taken from auditory-motor timing-related activations (synchronization vs. control condition) in Experiment 3 conducted with a different group of subjects.*

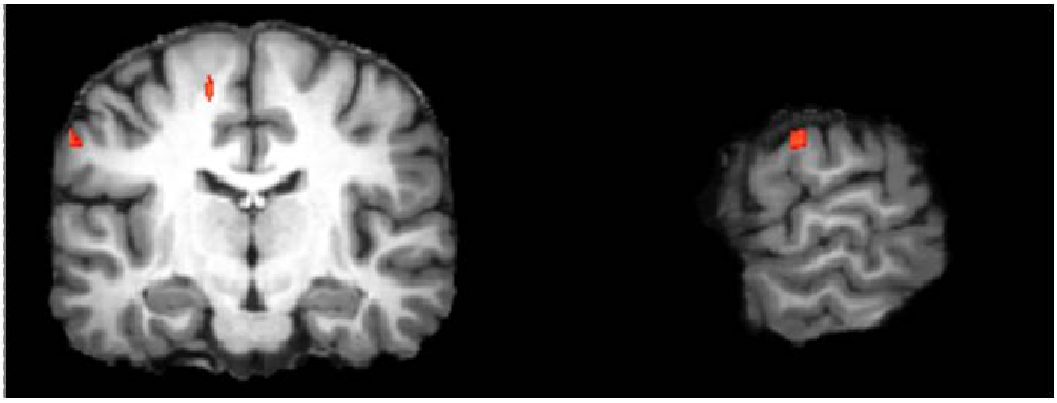

Figure A.4.: *Experiment 3: Activity increase in primary somatosensory areas for auditory-motor synchronization following rTMS over the left PMv.*

B. Tables

Table B.1.: *Experiment 2: Individual tempo preference after AG (baseline) and PMv stimulation across the whole experiment. Standardized regression coefficients (beta weights) for tempo, which describe the influence of this predictor on individual aesthetic judgments, were obtained by enter multiple regression. Because of the linear mathematical modelling, these beta weights provided information on the tendency of every subject to prefer rhythms with slow tempo (negative beta weights) or fast tempo (positive beta weights). Asterisk (*) indicates significant beta weights. Subjects are sorted according to the respective absolute value of beta weights for tempo in the AG session.*

Subject	Preferred Tempo	AG	PMv
		(beta weight)	**(beta weight)**
1	Slow tempo	-0.64*	-0.54*
2		-0.57*	-0.53*
3		-0.52*	-0.62*
4		-0.52*	-0.29*
5		-0.5*	-0.22*
6		-0.49*	-0.33*
7		-0.37*	-0.37*
8		-0.28*	0
9		-0.26*	-0.37*
10		-0.23*	-0.4*
11		-0.17*	-0.31*
12		-0.16*	-0.02
13		-0.16	-0.12
14		-0.05	-0.21*
15	Fast tempo	0.07	0.15
16		0.3*	-0.25*

Table B.2.: *Experiment 2: Individual linear mathematical models (individual case models) of judgment strategy computed to examine the influence of stimulus properties on aesthetic judgments after AG (baseline) and PMv stimulation. Standardized regression coefficients and multiple regression coefficients (R) as obtained by stepwise multiple regression are shown. Columns show all predictors of preference judgments (tempo, measure, beat subdivision, rhythmic figure and timbre; the latter two, being nominal, were assigned dummy variables.). Each subjects most important predictor for the judgment beautiful is in bold font.*

AG session

subject	tempo	measure	subdiv	rhythm	timbre	R
1						/
2	**-0.28**		-0.21			0.35
3	-0.26		-0.23		**0.48**	0.59
4	**-0.49**		**-0.49**		0.19	0.71
5	**-0.52**		-0.36		-0.30	0.70
6	**-0.52**		-0.39			0.65
7	**-0.64**		-0.32			0.72
8	-0.17		-0.29		**-0.67**	0.75
9					**-0.76**	0.77
10	-0.50		**-0.52**		0.19	0.75
11	-0.16		-0.21	-0.17	**-0.54**	0.62
12	-0.23		-0.18		**0.28**	0.40
13						/
14	**0.30**			0.19	-0.22	0.41
15	**-0.57**		-0.50			0.76
16	-0.37		-0.27	-0.16	**-0.45**	0.66

PMv session

subject	tempo	measure	subdiv	rhythm	timbre	R
1					**0.40**	0.40
2			**-0.26**		-0.19	0.32
3	-0.37		-0.17		**0.58**	0.71
4	-0.33		**-0.49**		-0.35	0.69
5	**-0.62**		-0.41		-0.19	0.77
6	-0.29		**-0.37**	-0.19		0.50
7	**-0.54**		-0.27		-0.20	0.64
8	-0.31				**-0.57**	0.65
9					**-0.51**	0.51
10	-0.22		**-0.60**			0.64
11					**-0.98**	0.98
12	**-0.40**				0.39	0.56
13	-0.21		**-0.25**			0.33
14	-0.25		**-0.41**			0.48
15	-0.53		**-0.58**			0.78
16	-0.37		**-0.46**			0.59

C. Task instructions

C.1. Experiments 1 and 2

Liebe(r) Versuchsteilnehmer(in),

Im folgenden Experiment werden Dir über Kopfhörer verschiedene Trommel- und Schlagzeugrhythmen vorgespielt. Jeder Durchgang beginnt dabei mit einem Hinweis, der eine der zwei möglichen Aufgaben anzeigt:

- **schnell?** Der Rhythmus soll auf sein Tempo hin beurteilt werden. Deine Aufgabe ist es, zu entscheiden, ob der Rhythmus eher schnell (”JA”/Zeigefinger) oder eher nicht schnell ist (”NEIN”/Mittelfinger).
- **schön?** Der Rhythmus soll auf seine Ästhetik hin beurteilt werden. Deine Aufgabe ist es, zu entscheiden, ob Du den Rhythmus eher schön (”JA”/Zeigefinger) oder eher nicht schön findest (”NEIN”/Mittelfinger).

Bitte drücke eine Antwort-Taste, sobald Du eine Entscheidung gefällt hast, jedoch noch während der Dauer des Rhythmus.

Beurteile die Rhythmen in Bezug auf Schnelligkeit und Schönheit bitte nicht im Vergleich zu anderen Klängen, Musikrhythmen und Musikstücken, sondern nur im Kontext der anderen Rhythmen dieses Experiments. Bewege Dich bitte nicht während der gesamten Dauer des Experiments.

Zur Übung gibt es einige Beispiele vor dem eigentlichen Experiment.

Hast Du noch Fragen? Vielen Dank für Deine Teilnahme!

C.2. Experiment 3

Liebe(r) Versuchsteilnehmer(in),

Im folgenden Experiment werden Dir über Kopfhörer verschiedene Klänge vorgespielt. Du wirst die Aufgabe bekommen, während der Klänge eine Taste wie folgt zu drücken:

- **Trommel- und Schlagzeugrhythmen**: Die Rhythmen haben alle einen regelmäßigen Grundschlag bzw. Beat, zu dem man sich bewegt. Deine Aufgabe ist es, den Beat des Rhythmus mit dem Zeigefinger der rechten oder der linken Hand (je nach vorhergehendem Hinweis) während der Präsentation des Rhythmus auf einer Antwort-Taste mitzudrücken.
- **Geräusche**: Die Geräusche haben im Gegensatz zu den Rhythmen keinen Beat. Deine Aufgabe ist es, mit dem Zeigefinger der rechten oder der linken Hand (je nach vorhergehendem Hinweis) während der Präsentation des Geräusches eine Antwort-Taste zu drücken. Drücke die Taste ungefähr so regelmäig wie während der Rhythmen.

Gelegentlich gibt es zwischen den einzelnen Durchläufen kurze Pausen.

Vor dem Experiment werden Dir die Hinweise erläutert und einige Beispielddurchläufe präsentiert, in denen Du die Aufgaben üben kannst. Zunächst wird zusätzlich ein Metronomschlag zu hören sein, der demonstriert, wann Du eine Antwort-Taste mitdrücken musst. Anschließend werden Beispieldurchläufe ohne Metronom präsentiert.

Hast Du noch Fragen? Vielen Dank für Deine Teilnahme!

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List of Abbreviations

µV	Microvolt
ACC	Anterior cingulate cortex
AG	Angular gyrus
ANOVA	Analysis of variance
BA	Brodmann area
BG	Basal ganglia
BOLD	Blood oxygen level dependent
FEF	Frontal eye field
fMRI	Functional magentic resonance imaging
FWHM	Full width at half maximum
HAPEM	Habitual pragmatic event map
HG	Heschl's gyrus
HRF	Hemodynamic response function
Hz	Hertz
IFG	Inferior frontal gyrus
M1	Primary motor cortex
MDEFT	Modified driven equilibrium Fourier transform
PCO	Precentral operculum
PD	Parkinson's disease
PMd	Dorsal premotor cortex
PMv	Ventral premotor cortex
P(r)	Probability of recognition
RF	Radio frequency
RMT	Resting motor threshold
ROI	Region of interest
RT	Reaction time
rTMS	Repetitive transcranial magnetic stimulation
rTMS-fMRI	Combination of rTMS and fMRI (offline)
SI/II	Primary and secondary somatosensory cortex
SE	Standard error
SMA	Supplementary motor area
SPT	Serial prediction task
STG	Superior temporal gyrus
T	Tesla
TE	Echo time
TMS	Transcranial magnetic stimulation
TR	Repetition time

Summary

Function of the ventral premotor cortex in auditory-motor integration of musical rhythm

KATJA KORNYSHEVA

The tendency of human beings to move in synchrony with an auditory rhythmical pulse is considered a human universal. Although progress has been made with regard to uncovering the neural underpinnings of speech and music during the last two decades in the advent of non-invasive neuroimaging techniques, it remains unknown, which neural mechanisms give rise to the urge and ability to accurately couple one's own movements to an auditory rhythm. The present thesis addresses the contribution of a motor-related brain region with prominent connections to auditory areas, the ventral premotor cortex (PMv), to auditory-motor integration of musical rhythm. The current work (i) probes the critical contribution of a motor-related region to both perceptual preference of and motor coupling to a musical rhythm, (ii) identifies additional neural mechanisms and networks that support auditory-motor timing and (iii) provides a neuroanatomically grounded model for auditory-motor integration of rhythm by incorporating the present experimental findings into a framework of sensorimotor cognition and control.

Using functional magnetic resonance imaging (fMRI), *Experiment 1* aimed at probing the involvement of motor-related brain regions when subjects' attention is directed to auditory rhythms they individually prefer compared to those that they do not. Specifically, the experiment was designed to test whether aesthetic appreciation of rhythms with individually preferred beat rate (tempo) around 2 Hz is accompanied by activity increase in the PMv which has been previously shown to be involved in rhythm perception tasks (H1). To test whether the hypothesized activity can be explained by increased internal auditory-motor simulation of the auditory beat rate, activity during preferred rhythms was compared to activity during a perceptual rhythm task (H2). In line with the notion of sensorimotor-driven forward models and previous evidence for the involvement of motor-related areas in perceptual rhythm tasks, it was assumed that the tempo judgment task required enhanced sensorimotor simulation. The obtained results revealed beat rate to be the most important temporal property of the musical rhythm with regard to the subjects aesthetic judgment. Importantly, musical rhythms with preferred beat rate but not with preferred timbre, a non-rhythmic property of the musical rhythms, engaged the left PMv confirming hypothesis H1. Moreover, the PMv activity increased to the same extent as during the perceptual rhythm task, lending support to the second hy-

pothesis (H2). The activity boost in the left PMv could not be explained by subjects humming along with the rhythm or by vocal imagery, since no significant activity increase was found in the supplementary motor area (SMA) or primary motor cortex. Importantly, the increase in PMv activity covaried linearly with how strongly the subjects preferred a certain beat rate.

Despite the results obtained in *Experiment 1*, it remained uncertain whether an interference with activity in the left PMv would affect the strength of beat rate preference. In *Experiment 2*, offline repetitive Transcranial Magnetic Stimulation (rTMS) was used in a similar experimental paradigm to probe the causal contribution of the left PMv to auditory beat rate preference. The individual beat rate preference strength and stability within and across sessions was hypothesized to be temporarily disrupted following rTMS interference with the left PMv (H3). Moreover, we assumed that the perceptual rhythm task, requiring the identification of the beat rate would also be affected (H4). As predicted (H3), rTMS over the left PMv temporarily interfered with individual beat rate preference strength depending on the the subjects' strength of tempo preference in the control session, i.e. subjects with most pronouced beat rate preference strength at baseline were more affected than subjects who showed weaker or no preference at all. Moreover, PMv stimulation temporarily disrupted the stability of individual beat rate preference strength within and across sessions. These effects were specific to the preference for beat rate in contrast to the preference for timbre and bound to the first half of the experiment following PMv stimulation. However, the hypothesis H4 was not confirmed by the results, since an interference with beat rate preference strength could not be explained by an impairment of beat rate recognition.

While *Experiments 1* and *2* revealed that a motor-related region - the left PMv - modulates auditory preference for a beat rate, it remained unclear whether this region is also critical for an accurate synchronization of movement to the auditory beat. If this were the case, perceptual preference for a beat rate would exploit the same auditory-motor integration resources as auditory-motor synchronization. Furthermore, an additional aim was to identify neural set of mechanisms, in particular, that of the contralateral right PMv that could potentially help to preserve auditory-motor timing. Accordingly, *Experiment 3* used the combination of offline rTMS and fMRI to determine the causal contribution of PMv to auditory-motor synchronization (H5) and identify task-dependent compensatory mechanisms that help to preserve task performance following its disruption (H6-H7). As expected, activity in the dorsal auditory stream - including Heschl's gyrus, posterior superior temporal gyrus and the PMv (BA6, extending into BA44) was enhanced for the synchronization compared to the control condition in all scans. Moreover, left PMv impaired auditory-motor synchronization, an effect that wore off with time according to H5. Although activity increased in the unaffected contralateral right PMv after left PMv stimulation confirming H6, it yet did not predict the behavioral effect of rTMS across subjects. Thus, for the right PMv, H7 was not supported. However, the subjects' performance after left PMv stimulation covaried negatively with task-specific activity in the anterior midline cerebellar region according to H7, an area previously associated with reduced response variability and discrete motor timing. In conclusion, the left PMv is causally relevant for auditory-motor integration. While activity increase in the ventral premotor region contralateral to the stimulation region did not help to preserve behavior, the anterior cerebellum could be linked to a compensation of auditory motor synchronization after PMv disruption.

The obtained results suggest that auditory-motor integration of rhythm relies on feed-forward computations in the PMv that predict both exafferent auditory and reafferent (somatosensory and proprioceptive) input. A stronger involvement of the PMv may induce the urge to alleviate the sensory mismatch between actual and predicted reafferent input by tuning-in to the auditory beat by body movement or vocalization.

Curriculum Vitae

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Eidesstattliche Versicherungen

Hiermit versichere ich, Katja Kornysheva, dass ich

1. nicht wegen eines Verbrechens zu dem ich meine wissenschaftliche Qualifikation missbraucht habe, verurteilt worden bin,
2. keine früheren Promotionsversuche unternommen habe,
3. die Dissertation nicht bereits anderweitig als Prüfungsarbeit vorgelegt habe,
4. die vorgelegte Dissertation selbst und ohne unerlaubte Hilfe angefertigt habe, sowie alle in Anspruch genommenen Quellen und Hilfsmittel in der Dissertation angegeben habe,
5. die Beschreibung der experimentellen Arbeiten, wie in der vorgelegten Dissertation gekennzeichnet, auf drei folgenden wissenschaftlichen Abhandlungen basiere und ich in allen als verantwortlicher Autor (”corresponding author”) gekennzeichnet bin, da ich *hauptverantwortlich* zur Entwicklung der Fragestellung und des experimentellen Designs, zur Datenerhebung und Datenauswertung, sowie zur Interpretation und Verfassung der hier genannten Manuskripte beteiligt war:

    - Kornysheva, K., von Cramon, D. Y., Jacobsen, T., & Schubotz, R. I. (2010b). Tuning-in to the beat: aesthetic appreciation of musical rhythms correlates with a premotor activity boost. Hum Brain Mapp, 31(1), 4864.
    - Kornysheva, K., von Anshelm-Schiffer, A.-M., & Schubotz, R. I. (in press). Inhibitory stimulation of the ventral premotor cortex temporarily interferes with musical beat rate preference. Hum Brain Mapp.
    - Kornysheva, K., & Schubotz, R. I. (submitted). Impairment of auditory-motor timing and compensatory reorganization after ventral premotor cortex stimulation.

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