Distinct systems for automatic and cognitively controlled time measurement: evidence from neuroimaging Penelope A Lewis and R Christopher Miall A recent review of neuroimaging data on time measurement argued that the brain activity seen in association with timing is not influenced by specific characteristics of the task performed. In contrast, we argue that careful analysis of this literature provides evidence for separate neural timing systems associated with opposing task characteristics. The 'automatic' system draws mainly upon motor circuits and the 'cognitively controlled' system depends upon prefrontal and parietal regions.
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Current Opinion in Neurobiology 2003, 13:250–255 This review comes from a themed issue on Cognitive Neuroscience Edited by Brian Wandell and Anthony Movshon 0959-4388/03/$ – see front matter DOI 10.1016/S0959-4388(03)00036-9 Abbreviations fMRI functional magnetic resonance imaging PMC lateral premotor area SMA supplementary motor area Introduction Every action we take and every stimulus we perceive has a temporal dimension. The neural mechanisms used to measure time are currently a topic of intensive investigation – the number of neuroimaging studies seeking to define and describe them is growing rapidly, including more than 20 studies published since the year 2000. To date, no strong consensus has been reached about which brain regions are involved in time measurement; however, a recent review [1] argues that the specific characteristics of the performed timing task do not affect the observed pattern of brain activity. Contrary to this, we suggest that much of the current ambiguity on the topic of neural time presentation may be due to the inappropriate grouping of studies that use very different time measurement tasks, thus drawing upon distinct neural timing systems. If this is the case, it should be possible to isolate the various neural systems involved in time measurement by a careful grouping of the literature, on the basis of the different task parameters used. In this review, we use precisely that approach, dividing studies of time representation according to three general task characteristics: the duration measured, the use of movement to define a temporal estimate, and the continuity and predictability of the task. The importance of stimulus characteristics Our decision to characterise studies in relation to interval duration and to use of movement builds on previous suggestions that these factors discriminate between two or more different time measurement systems. Evidence suggesting the existence of different neural systems for timing at different duration ranges includes: distinct psychophysical characteristics at different durations [2]; differential responses to pharmacological agents [2–6]; differential impairment of performance by dual task [7]; and, most recently, different patterns of brain activation during the measurement of sub-second and suprasecond intervals (PA Lewis, RC Miall, unpublished data). The timing of brief intervals is frequently linked with motor control because voluntary movements are typically of sub-second durations, and can be reproduced with extreme temporal consistency. The circuitry used to ensure this consistency is likely to be located within the motor system and may be used to measure brief intervals even in the absence of movement [8,9]. This timing could be accomplished using cortically modulated central pattern generators in the spinal cord, temporal pattern generation originating from the motor cortex [10–12], or temporally predictable changes in the activity of buildup cells: preparatory cells that gradually increase in activity prior to movement [13,14]. The cerebellum may also be involved in motor timing [15,16] and shows particularly appropriate circuitry for the measurement of brief intervals [17–20]. Our division of studies on the basis of interval length and involvement of movement therefore stems from the suggestion that motor circuitry may be involved in time measurement under some circumstances, specifically during the measurement of sub-second durations or durations defined by movement. Our division of studies according to the predictability and continuity of the time measurement task is rooted in two proposals. First, several authors have suggested that time measurements in the sub-

second range are automatic, whereas measurements in the multi-second range require attention [3,6]. Second, continually measuring intervals in a repeating cycle, or in a non-repeating but pre-learned and therefore predictable pattern, requires less direct attention than the discrete measurement of non-continuous trials. This proposal arises from studies of automatic movement showing that attention is not required for the performance of over-learned motor tasks [21]. The 250 Current Opinion in Neurobiology 2003, 13:250–255 www.current-opinion.com consistent timing achieved in these tasks [22] must also be performed in the absence of attention, and is very likely to draw upon an over-learned motor plan or programme [22,23]. Once selected and initiated, a motor programme can be executed without requiring direct attention. The measurement of a continuous series of predictable or over-learned movements should therefore require attention only during the selection and initiation phases. Taken together with the suggestion that motor circuitry can be used to measure temporal intervals even in the absence of movement, these two proposals suggest the preferential use of motor circuitry for continuous, predictable (as opposed to discontinuous or unpredictable) time measurement tasks. The hypothesis: automatic versus cognitively controlled timing On the basis of our predictions regarding how the three task characteristics discussed above draw on different neural resources, we propose that two distinct systems exist for measuring time in the types of behavioural tasks examined here. We also submit that each of the task characteristics discussed above helps to partially determine which system is active in any given task. One hypothesised system, which we will designate the 'automatic' timing system, is primarily involved in the continuous measurement of predictable sub-second intervals defined by movement. Automatic timing is likely to recruit circuits within the motor system that can measure time without attentional modulation. Central pattern generators would provide an ideal mechanism for this system, as they are characterised by continuous rhythmic output. The other hypothesised system, which we will designate the 'cognitively controlled' timing system, is more involved in the measurement of supra-second intervals not defined by movement and occurring as discrete epochs. Cognitively controlled timing is likely to draw upon multi-purpose cognitive circuits within the prefrontal and parietal cortices [24]; in particular, activity is expected in areas associated with attention and working memory [3,6,25,26]. Neuroimaging studies Figure 1 summarises the published neuroimaging literature on primate time measurement [PA Lewis, RC Miall, unpublished data, 1,9,14,27–47,48–52]. It lists the areas of brain activity reported in each study in response to time measurement tasks. Tasks are categorised according to whether or not a duration greater than one second was measured, whether measured intervals were defined by movement, and whether time measurement was continuous, with predictable intervals. The take home message is shown by the pattern of highlighted boxes in the figure: there is great variability between studies, but activity clusters in the upper left and bottom right corners of the table. Figure 2 shows the percentages of studies reporting activation in a given brain area as a proportion of all studies that imaged that area and used a particular combination of timing task characteristics. An important observation to make from Figure 2 is that the activity patterns observed when studies are divided according to combinations of task characteristics (Rows [b][i]) produce a more coherent picture, with a higher proportion of studies in a specific category activating the same areas, than the pattern observed when studies are combined across all categories (Row [a]). If diverse tasks all drew upon the same neural timing mechanism, we might expect a stronger consensus in Row (a). Because different networks appear to be activated by tasks with different combinations of characteristics (Rows [b][e] versus Rows [f][i]), the observed pattern strongly supports the possibility of anatomically distinct neural mechanisms in time measurement. Looking specifically at the categories emphasising automatic-related task characteristics (Rows [f][g]) we see very frequent activity in the motor system — the bilateral supplementary motor area

(SMA) and the left sensorimotor cortex are most commonly activated; the right cerebellum and lateral premotor area (PMC) are only slightly less frequently activated; the left thalamus and the basal ganglia are also activated. Activity in the right superior temporal gyrus is also common, whereas the prefrontal cortex and the majority of parietal cortices activate only rarely. Turning to the categories emphasising cognitive-controlrelated task characteristics (Rows [b][e]), we see that although some regions frequently observed in association with automatic timing (right PMC and bilateral SMA) also activate in these conditions, considerable activity occurs in the left cerebellum and in the prefrontal and parietal cortices, with a bias to the right cortical hemisphere. This pattern suggests that, although the use of the cognitively controlled system does not preclude involvement of some parts of the automatic system, additional areas are recruited for tasks with these characteristics. Before reading too much into the observed patterns, we should consider whether all of the activity discussed is truly associated with timing mechanisms or whether some of it might be due to confounding factors. Challenges to the hypothesis — confounds Because our analysis uses the most inclusive contrast from each dataset examined, much of the activity we describe may be due to task-related but non-temporal processes. Auditory, visual, and primary sensorimotor cortical activity found in association with automatic timing, for instance, might simply be due to sensory stimuli and motor responses. Some regions of the motor system, however, are active even in studies where very little Distinct systems for automatic and cognitively controlled time measurement Lewis and Miall 251 www.current-opinion.com Current Opinion in Neurobiology 2003, 13:250–255 Figure 1 000 111 1 1 1 1 1 1 000 1 11 1 1 X 1 X X X XX 000 1 1 11 1 1 1 1 1 000 111 11111111 111 11111 1 1 100 111111111 1111 111 1 1 1 1 100 1 X 1 1 X X 1 100 1 111 1 11 111 1 1 111 1 100 1111111 11 1 1 1 1 11 111 100 1 1 X 11 1 1 X 1 X 1111111 100 1 1 11 1 1 1 100 1 010 11111 1 1 1111 11 1 1 1 1 010 1 11111 1 1 1 010 1 1 1 11 1 1 001 1 111 1 11 1 1 1 001 1 X 1 X 1 X 1 1 1 1 001 1 1 1 001 11 111 1 1 1 001 11 1 1 1 1111 11 1 1 1 101 X X 1 X 1 1 11 101 111 1 11 1 1 1 1 101 1 1 1 1 1 1 1 1 1 11 101 1 1 1 11 1 101 1 1111 1 11 101 X 1 X X 1 1 101 1 X 11 1 11 X 1 1 X 1 1 011 1 X 1 1 X 1 X 1 11 X 1 1 X 1 X 1 X X 1 X 111 011 1 1 1 11 1 X 1 1 X 1 X X XX 111 1 11 111 1 111 1 1 111 1 1 111111111 111 1 1 11 111 1 1 11 1 11 1 11 111111 111 11 1 1 1 1111 111 11 1 1 1 1111 111 1 1 1 11 1 11 [a] [36] [44] [47] [14] [30] [31a] [31b] [32] [1] [52] [b] [29] [43] [9] [33] [50a] [50b] [51] [38] [39] [40] [41] [48a] [49a] [49b] [28] [37] [27] [34] [35] [45] [46a] [46b] [48b] REF Task RRRL L L L RRRRL RL R L RL RL L RL L L L L RRRL L Movement Short Continuous DLPFC IPS Insula CB Lat PMC IPS DLPFC Basal G VLPFC Thalamus F Pole Insula Inf Par VLPFC Cing CB Med Inf Par PMC Basal G S Par F Pole Cing CB Lat S Par Occip Thalamus S Temp SMA Occip SMA S Temp M1 S1 Current Opinion in Neurobiology Areas of activity reported in neuroimaging studies. Anatomical labels are listed across the top row of the figure, with laterality specified just above. Individual studies are listed row by row. Shaded cells within each row indicate areas of significant activity as reported by the authors. To be inclusive, we report results from the most lenient comparisons between conditions presented in each study (i.e. test versus rest, rather than a more rigorous control as in [31]). The annotation to Table 1 contains further details of the comparisons tested, or the comparisons we have selected. In papers reporting multiple datasets, each set is included as a separate row in the table (see [PA Lewis, RC Miall, unpublished data, 31,46,48–50]). We include one study of our own which is not yet published, but currently under review (PA Lewis, RC Miall, unpublished data). Several published studies were excluded [53,54 ,55 ,56 ,57] (see bibliographic annotations for details). Cells containing an X indicate that a brain region was not scanned; that cell is excluded from further calculations (Figure 2). Additional information on the references cited in Figure 1. (a,b) PA Lewis, RC Miall, unpublished data. 8 subjects indicated, via a button press, whether visually presented intervals were longer or shorter than standards (0.6 and 3 s,

in separate datasets). The control involved similar judgements regarding the physical length of a visual stimulus. We present fMRI data for time versus length comparisons at each duration. [1] Target intervals were presented by vibrotactile stimulation to the skin; the stimulation durations were reproduced by button pressing. We present data from the comparison of all timing conditions versus cued button pressing control. [9] Subjects indicated deviations in rhythm, pitch, or colour of auditory or visual stimuli. We merged results from auditory and visual rhythm monitoring versus pitch/colour monitoring. [14] We present fMRI data from the temporal production task versus cued button presses. [27] We report fMRI results from synchronisation versus rest. [28] We report PET signal increases during same/different judgements of auditory rhythms versus rest. Regions as specified by authors are used, as co-ordinates were not presented. [29] We present data from detection of long deviant sounds versus hearing standard length sounds. [30] We present data for the comparison of valid versus invalid duration feedback conditions in a temporal production task. [31] The spatial or temporal locus of a forthcoming instruction to move was pre-cued. We present time versus rest data from PET and fMRI experiments separately. [32] The time of a forthcoming cue to move was specified by valid or invalid pre-cues at two intervals. We present merged data from the contrast of all conditions versus rest. [33] All timing related activity reported is collapsed into one row of Table 1. [34] We collapse together results from synchronisation to auditory and visual cues versus rest continuation versus rest. [35] We have collapsed into a single row the results from all uni-manual tapping conditions versus rest, and from comparisons between the bimanual tapping tasks. [36] We present data from discrimination between tactile stimuli of different velocities versus rest. [37] We present results for temporal discrimination versus random button pressing control. [38] We report results from all self-paced tapping tasks versus rest. [39] We show results for memory-timed movements versus rest. [40] We report results from self-paced movement versus rest. [41] We report data from the synchronised versus cued press contrast. [43] We present data from temporal discrimination versus random response control. [44] PET data was presented separately for two monkeys, making temporal judgements versus spatial judgements; we merged the results from both. [45] Authors present PET data from isochronous production versus baseline, and repeated sequence versus isochronous, in both auditory and visual conditions. To be inclusive we list areas where signal increased in either contrast and in either modality. [46] We collapse results from synchronise, continue, listen, and discriminate versus rest, as the latter are included in the former, but report separately the two datasets for two intervals. [47] We present fMRI results from temporal discrimination tasks versus random button-press controls. Data was separated in 2.5 s epochs, but we list activity during any epoch. [48] We present separately the results of tapping synchronisation versus rest for long and short intervals, although both were acquired in a single experiment. [49] Subjects synchronised tapping with visual cues. Results for synchronisation at 5 s versus 0.6 s are presented separately for adults and adolescents. Results from an Attention Deficit Hyperactivity Disorder group are excluded. [50] Is formed from two experiments, which we present as separate lines in Table 1. In both, encoding of complex versus isochronous rhythms was compared. Results from these comparisons are merged for all rhythms presented in each experiment. [51] We report the fMRI data from 252 Cognitive Neuroscience Current Opinion in Neurobiology 2003, 13:250–255 www.current-opinion.com movement or movement preparation (and in some cases none at all) occurred during scanning. This is the case for activity in the right cerebellar hemisphere [29,36,50,51], the premotor cortex [28,33,40,51], the SMA [33,40,51], and the left basal ganglia [40,51,53], in timing tasks requiring only covert decisions, memory encoding, memory rehearsal of rhythms, or detection of oddballs. Because this activity is not due to movement (although motor imagery may occur), it may be genuinely linked to timing. Turning to the involvement of sensory

systems, several studies have described activity in the superior temporal lobe during time measurement tasks involving no auditory cues [27,30,32]. Others have shown auditory activity during task phases occurring after auditory cue cessation, such as continuation of tapping after auditory synchronisation [46], or memory encoding after presentation [50]. This activity may be associated with auditory imagery used for the task [46], and because it occurs most often in automatic timing tasks, specifically in those not involving supra-second intervals (Rows [g] and [h]), auditory imagery may be preferentially used under these circumstances. In contrast, the absence of occipital activity in tasks without visual stimuli makes it unlikely that this region is associated with temporal processing. The areas that commonly activate during cognitively controlled tasks include regions known for their involvement in working memory (e.g. the dorsolateral prefrontal cortex), recall (e.g. the ventrolateral prefrontal cortex), and attention (e.g. the intraparietal sulcus and inferior parietal lobe), all of which processes are believed necessary for cognitively controlled time measurement [3,6,25,26]. Because tasks associated with the cognitively Figure 2 RRRL L L L RRRRL RL R L RL RL L RL L L L L RRRL L DLPFC IPS Insula CB Lat PMC IPS DLPFC Basal G VLPFC Thalamus F Pole Insula Inf Par VLPFC Cing CB Med Inf Par PMC Basal G S Par F Pole Cing CB Lat S Par Occip Thalamus S Temp SMA Occip SMA S Temp M1 S1 34 26 29 50 46 26 29 24 40 18 26 17 49 23 31 29 23 46 32 15 14 20 54 18 32 24 11 58 24 61 29 45 33 Cognitively controlled timing 53 47 42 58 63 42 37 32 47 26 26 26 53 26 26 21 21 53 32 16 11 11 47 16 26 21 5 53 16 53 21 21 5 67 44 33 56 78 44 22 44 22 22 33 11 33 11 22 22 22 56 44 22 11 11 56 22 11 11 0 44 0 44 22 11 11 64 55 64 45 55 45 45 27 55 27 27 36 55 36 36 18 18 45 36 18 9 9 36 18 36 18 9 55 27 55 27 27 0 71 43 57 71 43 14 57 43 71 29 71 29 71 29 43 57 29 29 29 14 29 29 29 14 29 14 0 29 0 29 14 0 0 Automatic timing 13 0 13 19 25 6 19 13 31 6 25 6 44 19 38 25 25 38 31 13 19 31 38 19 38 25 19 56 31 63 38 69 63 0 0 0 14 14 0 0 0 14 0 14 14 29 0 14 29 14 57 43 29 14 0 57 29 43 43 29 86 43 86 71 100 100 11 0 0 22 22 0 11 11 22 11 22 11 33 11 22 33 22 56 44 22 22 11 56 33 33 44 33 67 33 67 67 89 89 7 0 14 14 21 7 14 7 29 0 21 7 43 14 36 21 21 36 29 14 14 29 36 14 43 21 14 64 36 71 36 71 64 Difference score (Rows [b]:[e]–[f]:[i]) 224 189 169 161 155 133 118 115 99 87 75 64 63 58 18 10 7 -4 -6 -7 -10 -12 -18 -24 -54 -69 -81 -93 -100 -106 -126 -270 -299 Any two cognitive elements No move, long Long, discrete No move, discrete Any two automatic elements Move, short Short, repeat Move, repeat (a) (b) (c) (d) (e) (f) (g) (h) (i) (j) (a) (b) (c) (d) (e) (f) (g) (h) (i) (j) Current Opinion in Neurobiology A summary of the activation patterns seen in Figure 1. The data from Figure 1 have been categorised by task characteristics. The percentages of studies reporting activity in specific regions in response to timing, calculated using only studies with the appropriate combinations of task characteristics, are indicated. More commonly activated regions are colour-coded from yellow (low activation) to red (high activation). For clarity, only areas that were active in at least 10% of all eligible studies are shown; many areas reported only in a minority of studies are therefore excluded from both figures. Row (a) shows the percentages of activity, calculated across all 35 datasets reviewed. Row (b) deals with studies in which any two of three task characteristics examined were associated with the cognitively controlled system. Rows (c)(e) specify the three possible pairings of characteristics. Rows (f)(i) follow a similar model, but for task characteristics associated with the automatic system. Columns are arranged from left to right by difference in the summed percentages in the cognitive tasks versus the automatic tasks (see Row [j]): those to the left are commonly activated in cognitive but not in automatic related tasks (grey cells in Row [j]), and vice versa for those on the right (blue cells in Row [j]); those in the centre are not strongly biased to either task type (white cells in Row [j]). Abbreviations as in Figure 1. (Figure 1 Legend Continued) encoding of rhythms versus the control condition, in which subjects ignored temporal information. [52] We present data from temporal measurement versus forward and backwards counting. [53]

The authors report PET studies of music performance, perception, and comprehension in musicians and non-musicians. These studies suggest that the neural systems underlying music are distributed throughout the left and right cerebral and cerebellar hemispheres, with different aspects of music processed by distinct neural circuits. However, this study is excluded from Figure 1 because a comprehensive list of activated regions is not provided. Abbreviations: Basal G, basal ganglia; CB Lat, lateral cerebellum; CB Med, medial cerebellum; Cing, cingulate (anterior and posterior) DLPFC, dorsolateral prefrontal cortex (includes Brodmann's areas 9 and 46); F Pole, frontal pole (includes Brodmann's area 10); Inf Par, inferior parietal gyrus; IPS, intraparietal sulcus; M1, primary motor area; Occip, occipital lobe; S1, primary somatosensory area; S Par, superior parietal gyrus; S Temp, superior temporal gyrus; VLPFC, ventrolateral prefrontal cortex (includes Brodmann's areas 45, 47, and 11). The SMA and the pre-SMA are combined as SMA; the frontal operculum is included in PMC [58], as are the frontal eye fields. The transverse temporal gyrus is included in superior temporal gyrus. Cerebellar nuclei are included in the appropriate cerebellar hemisphere. Where the laterality is not given, or is <5 mm, it is shown as bilateral. If localisations specified by authors are ambiguous (i.e. insula/operculum), they are indicated in both areas. Distinct systems for automatic and cognitively controlled time measurement Lewis and Miall 253 www.current-opinion.com Current Opinion in Neurobiology 2003, 13:250–255 controlled system are quite different from those associated with the automatic system, it could be argued that the prefrontal and parietal activities observed during the former, when lenient comparisons are applied, are due to confounding task characteristics — for example, memoryrelated or decision-related processes — rather than to time measurement alone. That these same regions are active even when more complete cognitive subtractions are used [PA Lewis, RC Miall, unpublished data, 14,47], however, suggests their genuine involvement in temporal processing. Conclusions A clear dissociation in brain activity related to timing is seen when neuroimaging studies of time measurement are divided according the interval to be measured, the use of movement to define time, and the continuity or predictability of the task. This dissociation cannot be explained by confounding task characteristics alone, and thus provides support for the existence of two distinct systems for time measurement. One, which we term the 'automatic' system, is closely linked to the motor and premotor circuits, with some involvement of the auditory cortex. This system does not draw much upon the prefrontal or parietal cortices. It may track time using temporal pattern generators, the temporally predictable increase or decrease of activity in build-up cells, or one of the various timing capabilities of the cerebellum. Auditory imagery may also be used. The other system, termed 'cognitively controlled', draws heavily upon the prefrontal and parietal cortices, which are likely to fulfil memory and attentional requirements, respectively. The prefrontal cortex is thought to be quite flexible in function, containing modules that can be recruited on demand for any one of several tasks [24]. It is possible that, although some timing functions can be performed within the less flexible neural circuits of the automatic system, direct attention to a timing task leads to the recruitment of flexible, multi-purpose modules to construct a more versatile, but temporary, clock system. Acknowledgements This work was supported by the Wellcome Trust and the Medical Research Council, UK. References and recommended reading Papers of particular interest, published within the annual period of review, have been highlighted as: of special interest of outstanding interest 1. Macar F, Lejeune H, Bonnet M, Ferrara A, Pouthas V, Vidal F, Maquet P: Activation of the supplementary motor area and of attentional networks during temporal processing. Exp Brain Res 2002, 142:475-485. This paper includes a review of recent timing studies, similar to the present one, but making the counter argument that the activation patterns seen do not support segregation of the neural systems by perceptual and motor tasks, nor by discrete and sequential timing tasks. The authors point to a core set of structures activated irrespective of

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Moving on Time: Brain Network for Auditory–Motor Synchronization is Modulated by Rhythm Complexity and Musical Training Joyce L. Chen1,2, Virginia B. Penhune2,3, and Robert J. Zatorre1,2 Abstract & Much is known about the motor system and its role in simple movement execution. However, little is understood about the neural systems underlying auditory–motor integration in the context of musical rhythm, or the enhanced ability of musicians to execute precisely timed sequences. Using functional magnetic resonance imaging, we investigated how performance and neural activity were modulated as musicians and nonmusicians tapped in synchrony with progressively more complex and less metrically structured auditory rhythms. A functionally connected network was implicated in extracting higher-order features of a rhythm's temporal structure, with the dorsal premotor cortex mediating these auditory–motor interactions. In contrast to past studies, musicians recruited the prefrontal cortex to a greater degree than nonmusicians, whereas secondary motor regions were recruited to the same extent. We argue that the superior ability of musicians to deconstruct and organize a rhythm's temporal structure relates to the greater involvement of the prefrontal cortex mediating working memory. & INTRODUCTION The ability to synchronize movements to a musical rhythm is a powerful but commonplace phenomenon: Most people will spontaneously tap their feet or nod along to the beat of a tune. In highly trained musicians, this skill reaches extraordinary levels, allowing a performer to execute complex movements with high temporal precision. Although a great deal is known about the motor system's involvement in simple movement execution, little is understood about the

neural systems underlying auditory–motor integration in the context of musical rhythm. In particular, it is unknown whether these systems are sensitive to the higher-order temporal structure contained in a musical rhythm, nor is it clear what underlies the enhancement of this capacity in musicians. In the present study, we use functional magnetic resonance imaging (fMRI) to investigate the neural mechanisms that underlie synchronization to varying levels of rhythm complexity, and we explore how these mechanisms are altered as a function of training that allows musicians to excel in timing movements to complex rhythms. A rhythm can be defined as a pattern of time intervals demarcated by sensory and/or motor events. Although movement synchronization is better to auditory than visual rhythms (Patel, Iversen, Chen, & Repp, 2005), little is understood about the neural substrates and mechanisms of these auditory–motor interactions. The ability to accurately reproduce and to synchronize to musical rhythm is dependent upon the temporal structure of the sequence, that is, the manner in which intervals of time marked by musical beats are organized (Essens & Povel, 1985). Metrical rhythms, where sequences can be subdivided into equal intervals of time, are better reproduced than nonmetrical rhythms, where sequences cannot be evenly partitioned in time (Grahn & Brett, in press; Essens & Povel, 1985). Thus, metrical rhythms may perhaps facilitate the ability to accurately encode, recall, and execute movement sequences because events can be temporally organized into smaller, chunked units, with each event falling in time with the temporal grid of an internally generated clock (Povel & Essens, 1985). The first goal of the present study is to parametrically manipulate the metrical structure of a rhythm in order to assess its behavioral and neural effect on movement synchronization and sequencing. In this study, we use the term synchronization in a general sense to convey the notion of the ability to time the onset of a motor response with the onset of an auditory event, and thus, the ability to reproduce rhythmic time intervals. Past studies have examined the neural correlates of movement synchronization to simple isochronous auditory rhythms (Pollok, Gross, & Schnitzler, 2006; Jancke, Loose, Lutz, Specht, & Shah, 2000; Rao et al., 1997). Others have parametrically manipulated physical aspects 1 McGill University, Montreal, Canada, 2 BRAMS Laboratory, Montreal, Canada, 3 Concordia University, Montreal, Canada D 2008 Massachusetts Institute of Technology Journal of Cognitive Neuroscience 20:2, pp. 226–239 of movement as an index of sequence complexity, and as expected, showed corresponding increases in motor activity (Dhamala et al., 2003; Haslinger et al., 2002; Harrington et al., 2000; Boecker et al., 1998; Catalan, Honda, Weeks, Cohen, & Hallett, 1998; Sadato, Campbell, Ibanez, Deiber, & Hallett, 1996). However, these paradigms may not be sensitive in revealing neural effects of musical training. One study (Lewis, Wing, Pope, Praamstra, & Miall, 2004) investigated temporal complexity by progressively increasing the number of different time intervals in a rhythm, but no change in performance as a function of the complexity manipulation was found. These aforementioned studies have shown that the neural regions involved in sequence and temporal complexity include the supplementary and presupplementary motor areas (SMA and pre-SMA, respectively), the dorsal premotor cortex (dPMC), the dorsolateral prefrontal cortex (DLPFC), the superior parietal lobule, and the cerebellum. Further, some of these regions are also implicated in the perception of metrical and nonmetrical rhythms (Sakai et al., 1999), as well as metrical rhythm reproduction from memory (Bengtsson, Ehrsson, Forssberg, & Ullen, 2004, 2005). The present study aims to establish a direct brain– behavior relationship between performance changes due to sequence complexity and neural activity, and to show that increases in motor activity as a function of complexity can be related to the motor system's ability to organize temporally complex information. A previous fMRI study conducted in our laboratory provides some evidence that the dPMC is involved in interactions between the auditory and motor systems during movement sequencing (Chen, Zatorre, & Penhune, 2006). In that study, we parametrically manipulated auditory features of a simple isochronous rhythm to increase its metric saliency.

As saliency increased, so did activity in the dPMC and auditory cortex with, in addition, increasing functional connectivity between these regions. These findings suggest that auditory regions may interact with the dPMC to accurately time the synchronization of movements to sounds. At present, models of auditory–motor interactions involving the dPMC have been formulated based on studies of speech/vocalizations and auditory spatial processing (Warren, Wise, & Warren, 2005; Hickok & Poeppel, 2004). Thus, the present study aims to extend results from our previous investigation (Chen et al., 2006) and thereby expand current knowledge about auditory– motor interactions. Studying musicians can allow us to examine how the brain changes in response to a focused and long-term training regime that is specific to the execution of intricately timed movement sequences. Synchronization to (Kincaid, Duncan, & Scott, 2002), and reproduction of, metrical (Drake, 1993; Franek, Mates, Radil, Beck, & Poppel, 1991; Smith, 1983) or nonmetrical (Watanabe, Savion-Lemieux, & Penhune, in press) rhythms is more accurate in musicians than nonmusicians. Furthermore, there is evidence for a greater cortical representation (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995) and gray matter concentration (Gaser & Schlaug, 2003) in motor-related regions of the brain for musicians. Finally, a number of studies have shown that compared to nonmusicians, musicians recruit smaller areas of activation in motor regions of the brain, such as the primary motor cortex, SMA, pre-SMA, premotor cortex, and cerebellum, suggesting that long-term training may result in a more efficient use of neural resources (Meister et al., 2005; Koeneke, Lutz, Wustenberg, & Jancke, 2004; Jancke, Shah, & Peters, 2000; Krings et al., 2000; Hund-Georgiadis & von Cramon, 1999). However, an important issue that arises from these studies is that no behavioral differences in measures of performance accuracy were demonstrated between the highly skilled musicians and subjects without musical training. This suggests that the dependent measures were not sensitive enough to detect differences, or that the simple unimanual movement sequences implemented in all of these studies were relatively easy for all participants to execute. In fact, the use of simple sequences to test for differences in musicians and nonmusicians, although relevant for examining carryover effects of long-term motor training to everyday skills, is unlikely an optimal paradigm to assess the specificity of musicianship. Thus, the paradigm developed for the present study uses a relatively complex rhythmic sequencing task that is specific to the skills a musician has acquired, and assesses whether this specificity is related to a particular pattern of neural activity different from that of nonmusicians. The present fMRI study aims to advance our knowledge about movement sequencing, auditory–motor interactions, and musicianship. First, we assess how manipulation of rhythm complexity can influence movement synchronization and examine the neural correlates mediating this behavior. The second goal evaluates how performance and neural activity differ between musicians and nonmusicians when the tested motor sequencing task is specific to those with musical training. A novel paradigm was implemented by parametrically manipulating the temporal structure of a rhythmic sequence for three levels (metric simple [MS], metric complex [MC], nonmetric [NM]), such that they became more temporally complex, and thus, less metrically structured (Figure 1). It is also possible that the nonmetric sequence can have structure imposed on it and thus, one could consider this rhythm type to be ambiguous. Subjects always first listened to a rhythm, and then tapped in synchrony with it during the next trial (Figure 2). We predicted that percent correct across the three levels of complexity and between-subject groups would not differ, indicating that all sequences were globally well learned by all subjects: It was paramount to ensure that any neural effect seen was not Chen, Penhune, and Zatorre 227 due to general complexity, effort in movement execution, or differences in motor learning. Critically though, we predicted that at the level of response synchronization, performance would progressively decrease as sequence complexity increased and that musicians would be better at synchronizing their motor responses with the

auditory cue than nonmusicians. Based on previous findings, we predicted the involvement of the SMA, preSMA, dPMC, DLPFC, and cerebellum in the sequencing of movements defined by temporal complexity. We also hypothesized that musicians should perform better than nonmusicians on our task and evaluated if this specialized subject group demonstrates a more efficient pattern of neural activity in motor-related regions of the brain, as has been suggested by previous studies. METHODS Subjects Twelve nonmusicians and 12 musicians (balanced for sex) participated in the study after giving informed written consent for a protocol approved by the Montreal Neurological Research Ethics Review Board. All volunteers were right-handed and healthy with normal hearing. Nonmusicians ranged from 20 to 32 years of age (mean = 23.83 years), had no musical training, and were either pursuing an undergraduate degree or had already obtained one. Musicians ranged from 19 to 28 years of age (mean = 23.17 years) and were categorized as musicians based on several criteria which ensured that they were highly skilled. Musical training commenced early between the ages of 3 and 10 years (mean = 5.5 years), with private instruction continuing up to the time of testing and an average of 17.67 years of training. Subjects were either pursuing a Bachelor's degree in music or had already obtained one. Categories of instruments played included strings, percussion, piano, woodwinds and brass. Stimuli and Conditions Subjects listened to and imitated three different auditory rhythms by tapping in synchrony on a computer mouse key with the index finger of the right hand (Figure 2). Figure 1. Schematic depiction of stimuli. Top row in each case shows the temporal sequence of events; bottom row shows the equivalent musical notation. All rhythms contained the same number and type of musical note durations, but arranged to create three levels of increasing metrical complexity: metric simple, metric complex, nonmetric. Figure 2. Representation of the fMRI sparse-sampling protocol. Each rhythm type was presented in a pair so that subjects first listened, then tapped with the same rhythm (only data for the tap trials were used for analysis). The three rhythm types were presented in a pseudorandom order, along with silence. 228 Journal of Cognitive Neuroscience Volume 20, Number 2 Each rhythm comprised 11 events (a woodblock sound), each 200 msec in duration. The interval following each sound was varied such that five different musical durations (onset-to-onset) would be created, each rhythm containing (in musical terminology): five eighth notes (each 250 msec), three quarter notes (each 500 msec), one dotted quarter note (750 msec), one half note (1000 msec), and one dotted half note (1500 msec). Thus, all rhythms were 6000 msec in duration with the same total number and type of notes, differing only in their temporal organization. This manipulation allowed us to create three rhythms with increasing metrical complexity (MS, MC, NM), based on rules of metric organization (Essens & Povel, 1985; Povel & Essens, 1985) (Figure 1). Pilot testing was first conducted on a separate group of 19 subjects in order to choose three rhythms from a sample of 12 that distinctly differed from each other with respect to complexity. There were a total of six test conditions as each rhythm type was associated with two tasks, ''listen'' and ''tap in synchrony.'' For listen trials, subjects only listened to the rhythms, without making any movements. During tapping trials, instructions were to tap as accurately as possible, synchronizing motor responses with each note of the rhythm (see Figure 2 for trial structure). Procedure Prescan To minimize the potential confound of motor learning during fMRI scanning, subjects were familiarized with the three test rhythms 1 day prior to the scan session. First, to address any non-task-specific effects, six easy rhythms were presented, defined based on their composition of three-beat repeating motifs (as opposed to the test rhythms with no recurring pattern). Subjects listened during the first trial and tapped in synchrony for the subsequent three trials. Next, each of the three test rhythms was presented in a block of 20 trials, each block randomized for order across subjects. Subjects listened during odd-numbered trials and learned to tap in synchrony for even-numbered trials. Lastly, 12 trials were given at the end of this session where each of the three test rhythms was

presented in two successive trials, pseudorandomized for order across subjects. Subjects listened during the first presentation and tapped in synchrony during the second presentation. Thus, the ''listen'' trial served as a prime for the ensuing ''tap in synchrony'' trial, ensuring that subjects knew which rhythm to tap to. This provided subjects with a preview of trial presentation during the fMRI session. Rhythms were presented at a comfortable intensity level through Sony headphones using Presentation software (version 0.8, from Neurobehavioral Systems) on a PC computer. Responses were made on the left mouse button using the right index finger and were recorded online. Scan Subjects were first given a block of 12 trials for practice, similar to the last set of trials carried out during the prescan session. During scanning, two runs were completed, each of which contained the six test conditions plus a silent baseline, for a total of seven conditions. The three rhythms were pseudorandomized in pairs by type (as described above), for presentation order within each run and across subjects. Two silent trials of the same duration as the rhythm trials were interspersed every six paired trials. Subjects were instructed that the beginning of each run commenced with a ''listen'' trial that was followed by a ''tap in synchrony'' trial, after which they would continue alternating between these tasks, with silent rest brakes interspersed (Figure 2). In the present study, only the data from the ''tap in synchrony'' trials were analyzed. Rhythms were presented binaurally through Siemens MR-compatible pneumatic sound transmission headphones at a sound intensity of 75 dB SPL using Presentation on a PC computer. All conditions were performed with eyes closed, and tap responses (key onset and offset times) were collected online. fMRI Acquisition Scanning was performed on a 1.5-T Siemens Sonata imager. High-resolution T1-weighted anatomical scans were collected for each subject (voxel size = 1 1 1 mm3 , matrix size = 256 256). Ninety-nine frames were obtained for each of two runs in the functional T2*-weighted gradient echo-planar scans (14 frames per condition per run). Whole head interleaved scans (n = 25) were taken, oriented in a direction orthogonal to that of the Sylvian fissure (TE = 50 msec, TR = 10,000 msec, voxel size = 5 5 5 mm3 , matrix size = 64 64 25, FOV: 320 mm2) (Figure 2). A single-trial sparse-sampling design (i.e., long TR) was used whereby scan acquisition occurred after each trial presentation. This ensured that the blood oxygenation level-dependent (BOLD) signal of the auditory stimuli would not be contaminated with the BOLD response of the acquisition noise (Belin, Zatorre, Hoge, Evans, & Pike, 1999). Furthermore, this paradigm avoids behavioral, and thus, neural interactions that may occur when auditory stimuli of a rhythmical nature are concurrently processed with the loud rhythmical scanner noise. Behavioral Analysis A global measure of accuracy assessed overall performance and ensured that all subjects were able to perform the task. Subjects' tap onset for each sound in the rhythm sequence was compared to the stimulus onset; a tap was deemed correctly executed when it occurred within half the onset-to-onset interval before or after the stimulus onset. If more than one tap Chen, Penhune, and Zatorre 229 response fell within the same window of time, the first response was taken and the second was excluded. Therefore, this measure globally informs us whether subjects knew the sequence, but critically, is not informative about the timings of each action within the sequence. Performance related to the specific skill of sensorimotor integration was assessed using more sensitive measures of synchronization ability, the intertap interval (ITI) and asynchrony. These dependent variables are appropriately suited to evaluate differences between groups and rhythm types because they assess specific aspects of performance and precisely tap into the cognitive process of interest. The ITI measures the ability to reproduce time intervals between each event in a sequence; it is a measure of period matching. We calculated the deviation (in absolute value) of a subject's ITI relative to the actual onset-to-onset interval, as a percentage score (% ITI deviation); the greater the deviation, the poorer the performance. Asynchrony assesses the ability to time the onset of a motor response with the onset of a stimulus event; in another

words, it is a measure of relative phase matching. For this measure, the absolute value of asynchrony was calculated because we were only interested in quantifying the amount of phase mismatch without regard for whether subjects were tapping ahead or lagging behind the stimulus event. Lastly, all dependent variables were calculated for each correct tap subjects made averaged across all trials for each rhythm type. After the experimental session, we also asked if subjects used any strategy to decode the rhythms, and thus, perform the task. fMRI Analysis The first volume of each functional run was discarded. Images from each scan were then realigned with the third frame as reference, motion corrected using the AFNI software (Cox, 1996), and smoothed using a 12-mm fullwidth half-maximum isotropic Gaussian kernel. For each subject, both anatomical and functional volumes were transformed into standard stereotaxic space based on the MNI 305 template. Statistical analysis of fMRI data was based on the general linear model with correlated errors, performed using an in-house tool called fMRISTAT (www.math.mcgill.ca/keith/fmristat) (Worsley et al., 2002). Group statistical maps were generated for each contrast of interest using a mixed-effects model (Worsley et al., 2002). To determine brain regions modulated by performance across the different levels of rhythm complexity, a covariation analysis was performed separately for each subject and then averaged for each group. Each individual subject's % ITI deviation score for each of the tapping conditions, averaged for each run, was used as the regressor variable. Thus, the parameter estimates represent the covariation of the BOLD response with increasing % ITI deviation. The tstatistical map assesses whether the slope of the regression line at each voxel is significantly different from zero. Positive t statistics show voxels whose activity increases as performance decreases and negative t statistics show voxels whose activity decreases as performance decreases. As a way to confirm the findings, and to quantify the changes in neural activity across conditions and between subject groups, the % BOLD signal change was extracted for voxels of interest (VOIs) from regions identified in this analysis, in each of the MS, MC, and NM tapping conditions, relative to silence, irrespective of the % ITI score. We also performed the above analyses using two other types of regressors: each subject's asynchrony score and a linear weighting of 1 to 3 that represented the rhythm complexity levels. To determine brain regions commonly recruited by nonmusicians and musicians from the covariation analysis, a conjunction analysis was performed. The conjunction analysis was implemented using the minimum of the t statistic obtained from the covariation contrast for each subject group (Friston, Penny, & Glaser, 2005). Thus, only those voxels from each contrast that survive a common threshold are considered significantly activated in the conjunction analysis. To address differences in neural activity between musicians and nonmusicians, a group subtraction analysis was carried out on the data for the covariation analysis, using a fixed effects model. This contrast thus assesses differences in the slope of the regression line between subject groups. For example, positive t statistics show neural regions that increase more in activity as performance decreases for musicians relative to nonmusicians. The % BOLD signal change was also extracted relative to silence at VOIs obtained from this analysis. To ascertain that regions identified in the covariation contrast are engaged in a network, a functional connectivity analysis was performed across all subjects because this type of analysis allows one to determine how neural activity at one prechosen seed voxel correlates with all other voxels in the brain across time. In modeling functional connectivity, the effects of the stimulus are accounted for, and data from the seed voxel are added as another confound to be solved for in the general linear model: Yij = Xib1j + Rib2j + >, where Yij is the voxel value at each frame i, for each voxel j; X contains the explanatory variables; b represents the parameter estimates; R represents data from the seed voxel; and > represents the error term. Slice timing correction is also implemented so that data from the seed voxel are resampled at the same frametimes and slicetimes as the fMRI data. The effect, standard deviation, and t statistic are then

estimated using fMRISTAT. The three tapping conditions (MS, MC, NM) used in the covariation analysis were inputted to the model for this analysis. Furthermore, the seed voxel was chosen from results of the conjunction analysis to ensure that it would be representative of both subject groups. This voxel was located in the dPMC and was 230 Journal of Cognitive Neuroscience Volume 20, Number 2 statistically the highest peak obtained from the conjunction analysis. Two additional functional connectivity analyses were performed for each subject group to specifically assess the temporal correlations between seed auditory regions with the dPMC. However, to ensure that the seed voxels would be common to the data set of both nonmusicians and musicians, they were chosen from the result of a conjunction analysis of the following contrast performed on the tapping conditions: 1/3(MS + MC + NM) silence. Peaks were evaluated using a general uncorrected value of $p < .0005$ (with particular focus on regions predicted a priori), that corresponded to a threshold of $t = 3.39$ for all analyses except the between-groups contrast where $t = 3.34$. Furthermore, because one goal of this study is to quantify similarities and differences in neural activation between musicians and nonmusicians, regions significantly activated in one subject group are also reported (if present) for the other. Anatomical localization of peak neural activity was classified using atlases (Schmahmann, Doyon, Toga, Petrides, & Evans, 2000; Duvernoy, 1991) and/or previously established criterion (Petrides, 2005; Picard & Strick, 2001; Westbury, Zatorre, & Evans, 1999). RESULTS Behavioral Results We used a repeated measures analysis of variance (ANOVA) to compare behavioral performance for musicians and nonmusicians across three levels of rhythmic complexity (MS, MC, NM). As predicted, global accuracy did not differ between subject groups [$F(1, 22) = 0.74$, $p = .40$] (musicians: MS = 92%, MC = 91%, NM = 89%; nonmusicians: MS = 89%, MC = 87%, NM = 88%). Similarly, there was no main effect of accuracy across the three rhythm types [$F(2, 44) = 1.24$, $p = .30$] and no interaction effect [$F(2, 44) = 0.70$, $p = .51$]. However, critically, measures of synchronization ability revealed that musicians were significantly more accurate in reproducing rhythmic intervals and synchronous in timing tap responses, than nonmusicians [% ITI deviation: $F(1, 22) = 14.88$, $p < .001$; asynchrony: $F(1, 22) = 15.86$, $p < .001$] (Figure 3). Furthermore, there was a significant main effect for rhythm type [% ITI deviation: $F(2, 44) = 12.56$, $p < .0001$; asynchrony: $F(2, 44) = 49.37$, $p < .0001$], where accuracy for interval reproduction and synchrony decreased as rhythm complexity increased (Figure 3). No interaction effect was present for the % ITI deviation measure [$F(2, 44) = 1.99$, $p = .15$], However, a significant interaction was found for the asynchrony measure [$F(2, 44) = 12.03$, $p < .0001$]: Tukey's post hoc comparison indicated that the MC and NM rhythm types were not significantly different from each other in the musician group [$ts(6, 44) = 1.66$, $p = .85$]. During debriefing, all musicians subjectively reported that they tried to fit the sequence with a metric structure, whereas nonmusicians reported chunking or grouping elements together. fMRI Results Covariation: Brain Regions Modulated by Temporal Complexity The results of the behavioral analyses demonstrated decreased synchronization ability as subjects tapped with increasingly complex rhythms. Therefore, % ITI deviation scores for each subject were regressed against neural activity across the three rhythm conditions to reveal brain regions whose activity was correlated with task performance. In nonmusicians, regions found to covary with increasing % ITI deviation scores included the following: pre-SMA, SMA, dPMC, ventral premotor cortex (vPMC), DLPFC, anterior cingulate cortex (ACC), inferior parietal lobule (IPL), thalamus, and cerebellum lobule VI (Table 1; Figure 4 where images are labeled under ''Nonmusicians''). In musicians, regions found to covary with changes in % ITI deviation across conditions were the same as those of nonmusicians (with the exception of the ACC), and in addition, the inferior frontal gyrus (BA 44/45) and cerebellum lobule VIIIa (Table 1; Figure 4 where images are labeled under ''Musicians''). These results were essentially identical to those using the asynchrony or

stimulus regressors and are thus not reported to avoid redundancy. However, it is important to note that convergence of these data allows us to suggest that performance is linked Figure 3. Percent ITI deviation and asynchrony measures for musicians and nonmusicians plotted across rhythm type. Data are reported as mean ± SE. Chen, Penhune, and Zatorre 231 with rhythm complexity because brain activity varied in a similar manner both with stimulus- and subject-driven properties. Lastly, none of the a priori regions of interest demonstrated a significant negative correlation. Conjunction: Brain Regions Similarly Recruited by Nonmusicians and Musicians Regions that were commonly modulated by metricality for both nonmusicians and musicians were determined by a conjunction analysis performed on data from the covariation analyses. Regions commonly activated included the dPMC and DLPFC (Table 1, Figure 4 where images are labeled under ''Conjunction''). Although below threshold, the pre-SMA, SMA, IPL, and cerebellum lobule VI were also similarly recruited in nonmusicians and musicians (Table 1, Figure 4). These findings were confirmed by a between-subjects repeated measures ANOVA on the % BOLD signal change values, extracted for peaks obtained from the covariation contrasts. These results showed no significant differences in neural activity between nonmusicians and musicians for any of these regions (see graphs in Figure 4). Subtraction: Differences between Musicians and Nonmusicians To determine how neural activity differed between nonmusicians and musicians in performance across rhythm complexity, a between-groups contrast was performed on the covariation data. The contrast musicians minus nonmusicians showed that neural activity in the following regions increased more as performance decreased in musicians: DLPFC (44, 38, 14), t = 3.37; Brodmann's area (BA) 44/45 (50, 14, 4), t = 3.44; cerebellar lobule VIIIa (30, 62, 44), t = 3.70 (Figure 5 where images are labeled under ''Musicians > Nonmusicians''). A between-subjects repeated measures ANOVA on % Table 1. Brain Regions Modulated by Temporal Complexity Nonmusicians Covariation Musicians Covariation Region (x, y, z) t (x, y, z) t Pre-SMA (BA 6)a (6, 6, 52) 4.28 (0, 4, 50) 2.42 (2, 18, 48) 3.98 (4, 16, 56) 2.84 SMA (BA 6)a (0, 2, 62) 3.84 (4, 2, 70) 2.31 dPMC (BA 6)a (22, 4, 60) 4.18 (28, 2, 58) 4.70 (14, 4, 62) 4.10 (42, 6, 54) 3.93 vPMC (BA 6) (42, 4, 46) 3.99 (30, 6, 44) 3.76 ACC (BA 32) (2, 20, 44) 4.04 DLPFC (BA 9/46, 46) (34, 50, 28) 3.50 (36, 50, 22) 4.10 Superiora (40, 40, 32) 3.50 (40, 36, 34) 2.92 Inferiorb (42, 42, 16) 3.95 IFG (BA 44/45)b (50, 12, 4) 3.98 IPL (BA 40)a (38, 60, 54) 3.23 (46, 50, 54) 4.25 (36, 54, 42) 4.45 (40, 52, 38) 3.94 Thalamusa (10, 18, 4) 3.23 (10, 18, 16) 3.94 Cerebellum: lobule VIa (36, 66, 28) 3.02 (28, 66, 28) 3.39 (8, 72, 26) 3.57 lobule VIIIab (32, 62, 44) 4.01 The stereotaxic coordinates of peak activations are given according to Talairach–MNI space, along with peak t values significant at $p < .0005$, uncorrected. BA = Brodmann's area; Pre-SMA = presupplementary motor area; SMA = supplementary motor area; dPMC = dorsal premotor cortex; vPMC = ventral premotor cortex; ACC = anterior cingulate cortex; DLPFC = dorsolateral prefrontal cortex; IFG = inferior frontal gyrus; IPL = inferior parietal lobule. a Regions commonly recruited in nonmusicians and musicians, as revealed by the conjunction analysis. b Regions that show more neural activity for musicians than nonmusicians. 232 Journal of Cognitive Neuroscience Volume 20, Number 2 BOLD signal change values obtained from VOI analyses at these peaks was also performed; results confirmed that musicians relative to nonmusicians demonstrated greater neural activity in the DLPFC [$F(1, 22) = 7.49$, $p < .05$] and a trend toward greater neural activity in BA 44/45 [$F(1, 22) = 3.90$, $p = .06$] (Figure 5). At the cerebellar peak in lobule VIIIa, there were no group differences [$F(1, 22) = 2.65$, $p = .12$], but a significant Figure 4. Brain regions modulated by temporal complexity. Results are shown for the covariation analysis for nonmusicians (column 1), musicians (column 2), and their conjunction (column 3). Regions where neural activity correlates with that of the dorsal premotor cortex (seed voxel) are shown in column 4 (Functional connectivity). Graphs in column 5 represent VOI analyses where the % BOLD

signal change is plotted across rhythm type for nonmusicians and musicians. Data are reported as mean ± SE. Color bar represents t values: range 10.0–5.0 (range 10.0–3.0 for cerebellum) for functional connectivity images; range 5.0–2.0 for all other analyses. Pre-SMA/SMA = presupplementary motor area/ supplementary motor area (row 1, sagittal view); dPMC = dorsal premotor cortex (row 2, horizontal view); IPL = inferior parietal lobule (row 3, coronal view); DLPFC = dorsolateral prefrontal cortex (row 4, coronal view); cerebellum (row 5, coronal view); MS = metric simple; MC = metric complex; NM = nonmetric. Chen, Penhune, and Zatorre 233 interaction effect was present [$F(1, 44) = 5.03$, $p < .05$] with greater signal change in the MC condition for musicians than for nonmusicians [Tukey's post hoc test; $ts(6, 44) = 8.24$, $p < .01$], and a general trend in the same direction for the other rhythm conditions (Figure 5). The contrast nonmusicians minus musicians showed neural activity in the medial posterior cingulate gyrus (6, 56, 16 and 4, 54, 20) and medial frontal BA 10 (0, 72, 10 and 4, 72, 8). More specifically, VOI analyses at these peaks revealed that nonmusicians demonstrated less deactivation (relative to silence) than musicians in these midline regions. Functional Connectivity: Distributed Network for Metrical Rhythm Processing A functional connectivity analysis was performed for all subjects, using a right dPMC peak obtained from the conjunction analysis as a seed voxel. This analysis allowed us to confirm whether the regions identified from the covariation analyses were indeed functionally related. Regions that temporally correlated across time with the right dPMC voxel included the following: left dPMC, vPMC, pre-SMA, DLPFC, IPL, precuneus, thalamus, anterior insula/inferior frontal operculum, and cerebellum lobule VIIIa (Table 2; Figure 4 where images are labeled under ''Functional Connectivity''). Functional Connectivity: Evidence for Auditory–Motor Temporal Coherence Based on the results from our previous study (Chen et al., 2006), which demonstrated functional connectivity between dPMC and secondary auditory regions, functional connectivity analyses were performed for each subject group exclusively to evaluate the temporal relationship Figure 5. Differences between musicians and nonmusicians. Results are shown for the covariation analysis for nonmusicians (column 1), musicians (column 2), and the group contrast musicians > nonmusicians (column 3). Note that musicians recruit two peaks in the dorsolateral prefrontal cortex (DLPFC; dashed lines). Rows 1 and 3 in coronal view, row 2 in horizontal view. Graphs in column 4 represent VOI analyses where the % BOLD signal change is plotted across rhythm type for nonmusicians and musicians. Data are reported as mean ± SE. Color bar represents t values; range 5.0–2.0 for all analyses. BA = Brodmann's area; MS = metric simple; MC = metric complex; NM = nonmetric. 234 Journal of Cognitive Neuroscience Volume 20, Number 2 between these regions in the present study. The seed auditory voxels were located in the planum temporale (66, 28, 16 and 46, 34, 18), at locations similar to the coordinates obtained from the previous study. Activity in the right auditory seed correlated with the right dPMC for nonmusicians, and bilaterally in this region for musicians (Table 2). The left auditory seed correlated with the right dPMC in both nonmusicians and musicians (Table 2). DISCUSSION Behavioral Results A novel aspect of our study is that we parametrically manipulated rhythm complexity using an auditory–motor synchronization paradigm, and showed that the ability to accurately time actions with an auditory cue depends on how successfully one can deconstruct the temporal structure of the sequence. Global accuracy was no different across levels of rhythm complexity for both subject groups, indicating that the sequences were well-learned and that all subjects were able to perform the task adequately. Therefore, any interpretation derived from the neuroimaging data could not be attributed to task difficulty for example, but rather, to specific parameters of performance such as the ability to synchronize movements with an auditory cue. As predicted, both musicians and nonmusicians demonstrated a decreased ability to accurately reproduce rhythmic intervals, and increased asynchrony while tapping to rhythms that become

progressively more complex; musicians also performed better than nonmusicians across all levels of rhythm complexity. It has been suggested that the superior performance of musicians stems from their ability to organize individual elements in a sequence within the context of the global temporal framework (Smith, 1983), a principle attributed to what is known as beat-perception in the field of music cognition. Thus, in conjunction with the subjective reports of our subjects, it is proposed that musicians use grouping strategies derived from higherorder knowledge of how musical time is structured, and this approach may consequently allow for a more accurate encoding of temporal information at each event in a sounded sequence. On the other hand, nonmusicians cannot use this type of top–down strategy, and thus, likely implement a bottom–up approach where individual elements in a sequence are grouped according to the Gestalt principle of temporal proximity; events that are close in time are chunked together (Bregman, 1999). This latter approach may hinder accurate encoding of temporal information at the event-by-event level, which would consequently result in an inferior ability to execute precisely timed movement sequences. Brain Regions Modulated by Temporal Complexity We manipulated the temporal structure of an auditory rhythm as an index of sequence complexity in order to modulate the ability to synchronize movements with these rhythms. Each subject's performance was regressed against BOLD signal change, thus critically, allowing us to make specific conclusions about brain– behavior relationships. In both nonmusicians and musicians, neural regions that showed increasing BOLD signal change as a function of performance included the pre-SMA, SMA, dPMC, DLPFC, IPL, and cerebellum lobule VI. Importantly, the results of the functional Table 2. Regions that Demonstrate Functional Connectivity with Seed Voxels in the Dorsal Premotor Cortex (dPMC) and Bilateral Planum Temporale (PT) Region (x, y, z) t Seed: dPMC (24, 2, 60) Pre-SMA (BA 6) (4, 18, 50) 9.42 dPMC (BA 6) (22, 0, 62) 9.62 vPMC (BA 6) (48, 8, 32) 8.24 (44, 0, 38) 5.48 DLPFC (BA 9/46, 46) (38, 28, 36) 9.58 (36, 28, 34) 6.69 (32, 48, 8) 3.64 IPL (BA 40) (44, 46, 44) 8.69 (38, 54, 50) 6.52 Precuneus (BA 7) (14, 66, 52) 7.11 (8, 40, 48) 5.12 (12, 66, 52) 6.32 Anterior insula/IFO (30, 18, 2) 4.24 Thalamus (16, 6, 8) 4.43 Cerebellum: lobule VIIIa (32, 64, 44) 3.40 Seed: PT (66, 28, 16) dPMC Nonmusicians (34, 14, 58) 3.98 Musicians (30, 14, 74) 3.41 (34, 14, 66) 3.57 Seed: PT (46, 34, 18) dPMC Nonmusicians (20, 18, 54) 3.95 Musicians (26, 10, 62) 4.23 (36, 18, 54) 4.55 The stereotaxic coordinates of peak activations are given according to Talairach–MNI space, along with peak t values, significant at $p < .0005$, uncorrected. BA = Brodmann's area; pre-SMA = presupplementary motor area; vPMC = ventral premotor cortex; DLPFC = dorsolateral prefrontal cortex; IPL = inferior parietal lobule; IFO = inferior frontal operculum. Chen, Penhune, and Zatorre 235 connectivity analysis provide strong evidence for involvement of these regions in a related network; activity in the seed dPMC voxel was shown to temporally correlate across time with all other regions modulated by the task. Because the number of movements and their timings are identical for each rhythm, our results identify a specific network of areas involved in the organization and sequencing of temporally complex movements, relevant for intricate action plans required during music performance. The role of the pre-SMA and SMA in the temporal organization of movements (Tanji, 2001), such as sequence chunking (Kennerley, Sakai, & Rushworth, 2004), is highly relevant to the present study because the strategy employed by all subjects relied upon the parsing of sequences, whether via a bottom– up (for nonmusicians) or top–down (for musicians) approach as discussed previously. The cerebellum, on the other hand, may facilitate the precision of these timed movements (Penhune, Zatorre, & Evans, 1998; Ivry & Keele, 1989), and the DLPFC and IPL may be involved in a prefrontal–parietal network for auditory (Zatorre, Mondor, & Evans, 1999) and temporal (Lewis & Miall, 2003) attention to the encoding and synchronization of temporal events. Current models of auditory–motor interactions have focused on the involvement of posterior auditory regions, and most of the

data supporting these models come from studies of speech (Hickok & Poeppel, 2004), and/or more general auditory feature processing such as space (Warren et al., 2005). This study makes a specific contribution concerning the role of the dPMC in rhythm sequencing; we propose that it is involved in the interfacing of auditory information with motor action in order to produce temporally organized movements. Past literature has already shown that the dPMC is critically involved in the discrete selection of movements based on conditional rules; these higher-order rules are conveyed or prompted by a sensory stimulus (Passingham, 1985; Petrides, 1985), leading some to propose a role for the dPMC in indirect sensorimotor transformations (Hoshi & Tanji, 2006; Wise, di Pellegrino, & Boussaoud, 1996). In the present study, we have proposed that musicians select movements based on higher-order rules of metricality, and nonmusicians select actions based on the Gestalt principles, or rules of grouping by temporal proximity. Neural activity in the dPMC increased as the ability to select movements, and thus, to synchronize accurately with auditory cues became more difficult, suggesting that subjects may have relied more on the dPMC as a guide to integrate the auditory cues with action. In our previous study, it was also demonstrated that neural activity in the dPMC increased as auditory features of a rhythm guiding movement selection progressively conveyed information of a higher-order nature, such as metric salience (Chen et al., 2006). Our work further suggests that the temporal accuracy in the integration of these sensory-guided movements may be mediated by the dPMC. This proposal is in line with results from a transcranial magnetic stimulation study (Davare, Andres, Cosnard, Thonnard, & Olivier, 2006) that found that the dPMC is critically involved in the timing of a visuomotor task requiring the coordination of a grasp with a concurrent lift. Lastly, results from the functional connectivity analysis confirm involvement of the dPMC in auditory–motor interactions; activity in the planum temporale is temporally correlated with activity in the dPMC, findings that replicate results from our previous study (Chen et al., 2006). Thus, our findings support and extend current models of auditory–motor interactions by demonstrating a direct link between activity in the planum temporale and the dPMC, in a musically relevant task. Similarities and Differences in Neural Activity between Musicians and Nonmusicians Having established the neural network involved in movement synchronization to auditory rhythms, we then further investigated whether this network differed in musicians who have had long-term practice on motor skills requiring fine sensorimotor coupling. Musicians were more accurate than nonmusicians at synchronizing motor responses with auditory cues, and neural activity in the pre-SMA, SMA, dPMC, and cerebellum lobule VI was similarly engaged in both subject groups across all conditions, as confirmed by the conjunction analysis. Furthermore, between-groups comparisons and VOI analyses did not reveal any differential neural activity in these motor-related areas. Our behavioral and neuroimaging findings are in contrast to previous studies comparing musicians and nonmusicians on unimanual motor sequencing tasks (Meister et al., 2005; Koeneke et al., 2004; Jancke, Shah, & Peters, 2000; Krings et al., 2000; Hund-Georgiadis & von Cramon, 1999). These studies have shown that musicians recruit a smaller network of neural activity in secondary motor regions and the cerebellum, and they have put forth the interpretation that this reduced activity is the result of a more efficient neural organization derived from their longterm training on motor skills. However, the findings in the present study suggest that, for a motor sequencing task requiring accurate synchronization of movements with sounds, secondary motor regions and cerebellar lobule VI are not differentially recruited. Instead, musicians recruit the DLPFC and BA 44/45 to a greater extent than nonmusicians, a finding we attribute to the superior ability of musicians to track, retrieve, manipulate, and thus, organize temporal information. The task utilized in this experiment relies upon an ability to sequence rhythmic events, a skill specific to training acquired by musicians. However, the tasks implemented in the previous studies tested basic motor abilities that nonmusicians and musicians alike

possess (e.g., sequential finger–thumb opposition, tapping with one finger 236 Journal of Cognitive Neuroscience Volume 20, Number 2 or each finger sequentially), which could thus account for the lack of performance difference between subject groups. Therefore, musicians may demonstrate a more ''efficient'' recruitment of motor neural regions, but only when the experimental tasks used are nonspecific to musicianship. We suggest that when a task is designed to tap into skills specific to musicianship, such as that used in the present study, then we are testing the ''competency,'' rather than ''efficiency,'' of the neural system in response to that task, and that musicians should activate neural regions specific to the tested skill. Similarly, studies have demonstrated enhanced recruitment of auditory regions in musicians compared to nonmusicians when the stimuli used are specific to musicianship (Schneider et al., 2002; Pantev et al., 1998). The between-groups contrast also revealed one peak in lobule VIIIa of the cerebellum that showed more neural activity in musicians than nonmusicians for the metric complex condition, and a trend toward group differences in the same direction for the other conditions. Because this peak was located in the left cerebellar hemisphere, it is unlikely related to the mere act of motor execution that would recruit ipsilateral neural activity corresponding to right-finger tapping. Instead, one could hypothesize that musicians, by nature of their specific training, would demonstrate superior abilities in timing and error correction (Penhune et al., 1998), and general auditory discriminative processes (Petacchi, Laird, Fox, & Bower, 2005), roles attributed to the cerebellum that may be related to the greater gray matter cerebellar concentration in musicians than in nonmusicians (Gaser & Schlaug, 2003). We argue that activity in the right DLPFC and right BA 44/45 is directly related to the behavioral advantage demonstrated by musicians because these regions were revealed by a group contrast of the covariation analysis, which itself, is a regression using each individual's behavioral score. Although nonmusicians recruited the DLPFC, musicians additionally recruited another DLPFC peak that was more inferiorly located. One could interpret this additional peak of activity as just an extension of its involvement in the prefrontal–parietal network related to temporal attention processing previously discussed. However, there is also an alternative interpretation when one considers the role of the DLPFC in conjunction with that of BA 44/45. The DLPFC and the ventrolateral prefrontal cortex (VLPFC), which includes BA 45, are critical nodes involved in a dorsal–ventral model of working memory function (Petrides, 2005). In this model, sensory information that is held in the posterior association cortices is actively retrieved by the VLPFC, and manipulation or monitoring of this information is mediated by the DLPFC. In the context of rhythmic sequencing, we propose that the VLPFC is involved in extracting the correct temporal information (i.e., beat duration) related to each of the 11 elements comprising the sequence, and that the DLPFC may be concomitantly involved in keeping track or monitoring which of the 11 temporal durations is the next in the sequence to be retrieved for movement synchronization. It has also been suggested that Broca's areas 44 and 45 are involved in a structured hierarchy of action selection, independent of temporal arrangement (Koechlin & Jubault, 2006), and could be involved in auditory–motor interactions (Lahav, Saltzman, & Schlaug, 2007). Neural activity in BA 44 may mediate the selection of simple action chunks, whereas BA 45 may be implicated in the superordinate organization of these simple action chunks (Koechlin & Jubault, 2006). As discussed previously, musicians have a priori knowledge about how rhythms are structured in time, and therefore, we propose use of a top–down strategy, whereby elements in a sequence are recoded into smaller chunks following the rules of metric organization. The enhanced ability to retrieve, monitor, and thus, chunk information confers a behavioral advantage for the musicians over nonmusicians and may be accounted for by greater neural activation in the DLPFC and VLPFC. Acknowledgments We thank Marc Bouffard for consultations on the fMRI analysis and computer programming of the behavioral task, Evgueni Lapidous for

implementation of an algorithm for behavioral data analysis, and the staff at the McConnell Brain Imaging Centre for their technical assistance. This work was supported by grants from the Canadian Institutes of Health Research, Natural Science and Engineering Research Council, and a McGill Major Fellowship to J. L. C. Reprint requests should be sent to Joyce L. Chen, Rm. 276, 3801 University St., Montreal, QC H3A 2B4, or via e-mail: joyce.chen@mail.mcgill.ca. REFERENCES Belin, P., Zatorre, R. J., Hoge, R., Evans, A. C., & Pike, B. (1999). Event-related fMRI of the auditory cortex. Neuroimage, 10, 417–429. Bengtsson, S. L., Ehrsson, H. H., Forssberg, H., & Ullen, F. (2004). Dissociating brain regions controlling the temporal and ordinal structure of learned movement sequences. European Journal of Neuroscience, 19, 2591–2602. Bengtsson, S. L., Ehrsson, H. H., Forssberg, H., & Ullen, F. (2005). Effector-independent voluntary timing: Behavioural and neuroimaging evidence. European Journal of Neuroscience, 22, 3255–3265. Boecker, H., Dagher, A., Ceballos-Baumann, A. O., Passingham, R. E., Samuel, M., Friston, K. J., et al. (1998). Role of the human rostral supplementary motor area and the basal ganglia in motor sequence control: Investigations with H2 15O PET. Journal of Neurophysiology, 79, 1070–1080. Bregman, A. (1999). Auditory scene analysis, the perceptual organization of sound. Cambridge: MIT Press. Catalan, M. J., Honda, M., Weeks, R. A., Cohen, L. G., & Hallett, M. (1998). The functional neuroanatomy of simple and complex sequential finger movements: A PET study. Brain, 121, 253–264. Chen, J. L., Zatorre, R. J., & Penhune, V. B. (2006). Interactions between auditory and dorsal premotor cortex during Chen, Penhune, and Zatorre 237 synchronization to musical rhythms. Neuroimage, 32, 1771–1781. Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Computers and Biomedical Research, 29, 162–173. Davare, M., Andres, M., Cosnard, G., Thonnard, J. L., & Olivier, E. (2006). Dissociating the role of ventral and dorsal premotor cortex in precision grasping. Journal of Neuroscience, 26, 2260–2268. Dhamala, M., Pagnoni, G., Wiesenfeld, K., Zink, C. F., Martin, M., & Berns, G. S. (2003). Neural correlates of the complexity of rhythmic finger tapping. Neuroimage, 20, 918–926. Drake, C. (1993). Reproduction of musical rhythms by children, adult musicians, and adult non-musicians. Perception & Psychophysics, 53, 25–33. Duvernoy, H. M. (1991). The human brain: Surface, threedimensional sectional anatomy and MRI. New York: Springer-Verlag. Elbert, T., Pantev, C., Wienbruch, C., Rockstroh, B., & Taub, E. (1995). Increased cortical representation of the fingers of the left hand in string players. Science, 270, 305–307. Essens, P. J., & Povel, D. J. (1985). Metrical and nonmetrical representations of temporal patterns. Perception & Psychophysics, 37, 1–7. Franek, M., Mates, J., Radil, T., Beck, K., & Poppel, E. (1991). Finger tapping in musicians and nonmusicians. International Journal of Psychophysiology, 11, 277–279. Friston, K. J., Penny, W. D., & Glaser, D. E. (2005). Conjunction revisited. Neuroimage, 25, 661–667. Gaser, C., & Schlaug, G. (2003). Brain structures differ between musicians and non-musicians. Journal of Neuroscience, 23, 9240–9245. Grahn, J. A., & Brett, M. (2007). Rhythm and beat perception in motor areas of the brain. Journal of Cognitive Neuroscience, 19, 893–906. Harrington, D. L., Rao, S. M., Haaland, K. Y., Bobholz, J. A., Mayer, A. R., Binder, J. R., et al. (2000). Specialized neural systems underlying representations of sequential movements. Journal of Cognitive Neuroscience, 12, 56–77. Haslinger, B., Erhard, P., Weilke, F., Ceballos-Baumann, A. O., Bartenstein, P., Grafin von Einsiedel, H., et al. (2002). The role of lateral premotor–cerebellar–parietal circuits in motor sequence control: A parametric fMRI study. Brain Research, Cognitive Brain Research, 13, 159–168. Hickok, G., & Poeppel, D. (2004). Dorsal and ventral streams: A framework for understanding aspects of the functional anatomy of language. Cognition, 92, 67–99. Hoshi, E., & Tanji, J. (2006). Differential involvement of neurons in the dorsal and ventral premotor cortex during processing of visual signals for action planning. Journal of Neurophysiology, 95, 3596–3616. Hund-Georgiadis, M., & von

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The sensation of groove engages motor and reward networks

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Abstract

The sensation of groove has been defined as the pleasurable desire to move to music, suggesting that both motor timing and reward processes are involved in this experience. Although many studies have investigated rhythmic timing and musical reward separately, none have examined whether the associated cortical and subcortical networks are engaged while participants listen to groove-based music. In the current study, musicians and non-musicians listened to and rated experimentally controlled groove-based stimuli while undergoing functional magnetic resonance imaging. Medium complexity rhythms elicited higher ratings of pleasure and wanting to move and were associated with activity in regions linked to beat perception and reward, as well as prefrontal and parietal regions implicated in generating and updating stimuli-based expectations. Activity in basal ganglia regions of interest, including the nucleus accumbens, caudate and putamen, was associated with ratings of pleasure and wanting to move, supporting their

important role in the sensation of groove. We propose a model in which different cortico-striatal circuits interact to support the mechanisms underlying groove, including internal generation of the beat, beat-based expectations, and expectation-based affect. These results show that the sensation of groove is supported by motor and reward networks in the brain and, along with our proposed model, suggest that the basal ganglia are crucial nodes in networks that interact to generate this powerful response to music.

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Keywords

GroovefMRIBeatRhythmic complexityBasal gangliaReward

1. Introduction

The sensation of groove, defined as the pleasurable desire to move to music (Janata et al., 2012), is one of the most powerful sources of music-derived pleasure. One way in which music is thought to elicit pleasure is through the interplay between the violation and fulfillment of musical expectations (Cheung et al., 2019; Huron, 2006; Juslin and Västfjäll, 2008; Meyer, 1956; Salimpoor et al., 2015). Musicians and composers can manipulate the expectations of a listener by altering the complexity or predictability of the rhythms, melodies, harmonies, or other factors that make up a piece of music. For example, listeners prefer melodies that are moderately complex (i.e., moderately unpredictable) compared to very simple or very complex melodies (Pearce and Wiggins, 2012). Similarly, groove is thought to rely predominantly on rhythmic expectations, with moderately complex rhythms leading to greater pleasure and wanting to move (Matthews et al., 2019; Sioros et al., 2014; Witek et al., 2014).

Rhythmic expectations are closely tied to the metre, which is the pattern of alternating strong and weak beats (London, 2012; Vuust and Witek, 2014). For example, in a waltz metre which consists of a strong beat followed by two weak beats, listeners will expect a note to fall on the strong beat. When notes fall between beats, or on weak beats rather than strong beats, they create syncopations which violate expectations and challenge the metre (Fitch and Rosenfeld, 2007; Vuust and Witek, 2014). Very simple rhythms with no syncopations are highly predictable, but boring, as most, if not all rhythmic

expectations are confirmed. Highly complex rhythms, with many syncopations, are unpredictable and hard to follow as it is difficult for the listener to perceive a metre, and thus generate rhythmic expectations. Medium complexity rhythms, with some syncopations, strike a balance allowing for both the formation and violation of rhythmic expectations. As the metre is challenged by syncopations, rhythmic expectations need to be assessed and updated. It has been proposed that this continuous engagement of rhythm expectation processes drives the pleasure associated with groove (Koelsch et al., 2019; Vuust et al., 2018; Vuust and Witek, 2014). One way of assessing rhythmic expectations is through movement (Patel and Iversen, 2014), which may account for the desire to move associated with groove (Koelsch et al., 2019).

The link between rhythmic expectations and wanting to move suggests that motor regions of the brain may be involved in processing groove-based music such as funk, Afro-Cuban, and hip-hop (Danielsen, 2006; Greenwald, 2002). There have been no previous neuroimaging studies investigating the brain regions involved in the sensation of groove. However, studies of beat perception show activity in brain networks associated with auditory-motor integration and motor timing (Araneda et al., 2016; Bengtsson et al., 2009; Burunat et al., 2017; Chapin et al., 2010b; Chen et al., 2008; Grahn and Brett, 2007; Grahn and Rowe, 2013, 2009; Kung et al., 2013; Schubotz et al., 2000; Thaut et al., 2014). The basal ganglia (BG) seem to be particularly important for beat perception as they are crucial nodes in a core timing network proposed to underlie beat-based timing (Matell and Meck, 2004; Merchant et al., 2015; Teki et al., 2011). The BG also form distinct cortico-striatal circuits that may support different motor and motivational functions relevant to groove (Alexander et al., 1986; Haber, 2003). Recent studies have demonstrated that the putamen and supplementary motor area (SMA), which are parts of the cortico-striatal 'motor circuit', show selective responses to beat and metre (Araneda et al., 2016; Li et al.,

2019). The caudate forms circuits with both prefrontal and parietal regions (Jarbo and Verstynen, 2015) and has been implicated in both rhythmic (Trost et al., 2014) and harmonic expectations (Seger et al., 2013).

Premotor, prefrontal, and parietal regions are also often activated in response to a strong beat (Bengtsson et al., 2009; Danielsen et al., 2014; Grahn and Schuit, 2012; Grahn et al., 2011; Grahn and McAuley, 2009; Grahn and Rowe, 2009; McAuley et al., 2012; Schubotz et al., 2000; Schubotz and von Cramon, 2001). These regions are part of the dorsal auditory stream (Hickok and Poeppel, 2004; Rauschecker, 2011), while premotor and parietal regions together form the dorsal fronto-parietal network (Ptak et al., 2017). These networks are believed to underlie abstract motor representations that allow for integration of sensory information over time (Ptak et al., 2017; Rauschecker, 2011). Furthermore, rhythmic expectations can be thought of as temporal predictions which are thought to originate in the motor and premotor cortices (Morillon and Baillet, 2017; Rimmele et al., 2018) and may reflect covert action simulation (Arnal, 2012; Patel and Iversen, 2014; Ross et al., 2016; Schubotz, 2007). Therefore, groove may activate motor regions of the brain via both the motor processes underlying rhythmic expectations and the overt or covert movement preparation purportedly involved in testing these expectations. Consistent with this, motor cortical excitability has been found to be greater for high compared to low groove music (Stupacher et al., 2013).

In addition to their role in beat-based timing, the BG, particularly the caudate and nucleus accumbens (NAcc), are associated with the anticipation and experience of music-derived pleasure (Blood et al., 1999; Blood and Zatorre, 2001; Koelsch, 2014; Salimpoor et al., 2013, 2011). Activity in the NAcc has been associated with the experience of pleasure including from primary (e.g., food and sex) and secondary (e.g.,

money) rewards (Sescousse et al., 2013). During music-listening, the NAcc is active during moments of peak pleasure, while the caudate is active in the period just before peak pleasure, suggesting that the caudate is involved in the anticipation of pleasure (Salimpoor et al., 2011). The medial orbitofrontal cortex (mOFC) also plays a role in assigning, maintaining and monitoring the value of a stimulus (Kringelbach, 2005; O'Doherty, 2004), including music (Koelsch, 2014). A network formed by the NAcc, mOFC, and auditory cortex has been linked to the enjoyment of music as shown by both structural (Martinez-Molina et al., 2019) and functional (Salimpoor et al., 2013) connectivity measures.

Taken together, the sensation of groove can be framed as the intersection of reward processing and the motor processes that underlie beat perception, with rhythmic expectations as the driving mechanism. Therefore, to test the role of both reward and motor networks in the experience of groove, we asked participants to listen to rhythms with medium and high levels of complexity (i.e., degree of syncopation), and rate both their desire to move and pleasure while undergoing functional magnetic resonance imaging (fMRI). Stimuli were drawn from a previous behavioural study showing that medium complexity rhythms were rated as more pleasurable and elicited a greater desire to move compared to low and high complexity rhythms (Matthews et al., 2019). Because we also found that harmonic complexity modulated the affective component of groove, this factor was included here. Finally, we tested both musicians and non-musicians based on evidence that training can affect both the sensation of groove (Matthews et al., 2019; Senn et al., 2018) and neural processing in both auditory-motor (Alluri et al., 2017; Grahn and Brett, 2007; Grahn and Rowe, 2009) and reward networks (Alluri et al., 2015; Chapin et al., 2010a).

We expected medium complexity stimuli to elicit activation in brain networks involved in the processing of musical beat, as well as in cortical and striatal regions linked to reward, with

stronger effects in musicians than non-musicians. Given the roles of the putamen, caudate, and NAcc in beat-based timing and reward, we focused analysis on these regions of interest.

2. Material and methods

2.1. Participants

Fifty-seven participants were recruited into two groups (musicians and non-musicians). Musicians had a minimum of eight years of training and were currently practicing. Non-musicians had less than one year of training and were not currently practicing. Informed consent was obtained, and the study was approved by the Central Denmark Region Committees on Health Research Ethics. Participants received 200 DKK remuneration. Two non-musicians were excluded from the scanning session due to technical problems. Another non-musician was excluded as their ratings showed no variability. Demographic data for the final sample are provided in Table 1.

Table 1. Participant demographic data.

Empty Cell	**Non-Musicians**	**Musicians**
N (male/female)	25 (13/12)	29 (17/12)
Age (SD)	23.20 (2.46).	23.76 (2.84)
Years of musical training (SD)	0.16 (0.31)	11.5 (3.27)
Hours of music practice per week (SD)		11.67 (10.20)

2.2. Stimuli

The stimuli were a subset of those developed and validated in a previously reported online study (Matthews et al., 2019). The stimuli consisted of short musical sequences with two levels of both rhythmic and harmonic complexity. There were three rhythms and three chords for each level of complexity resulting in 36 unique stimuli of four different categories: medium rhythm/medium harmony (Mr-Mh), medium rhythm/high

harmony (Mr-Hh), high rhythm/medium harmony (Hr-Mh), and high rhythm/high harmony (Hr-Hh). These levels of complexity were chosen since, in the previous study, medium levels of rhythmic and harmonic complexity elicited the highest ratings and showed the greatest difference in ratings compared to high complexity rhythms and chords. In addition, two rather than three levels of complexity were chosen in order to maximize the number of trials for each level. The stimuli were created using Cubase Pro version 8.0.30 (Steinberg Media Technologies).

The sequences consisted of piano chords organized into rhythmic chord patterns in a piano timbre presented at 96 beats per minute. Each sequence was 10 s long and contained four repeats of a five-onset rhythm pattern with a single chord repeating throughout each sequence plus an isochronous eighth-note hi-hat pattern (see Fig. 1 for musical notation of a medium complexity rhythm and SFig. 1 for a schematized representation of all rhythm patterns). The medium complexity rhythms consisted of two Afro-Cuban rhythms known as the son clave and rumba clave, and one experimenter-created rhythm. The high complexity rhythms had all but the first onsets shifted to be early or late relative to the medium complexity patterns, thus increasing their rhythmic complexity. Rhythmic complexity was quantified using the syncopation index (Fitch and Rosenfeld, 2007). As the hi-hat pattern was identical for all stimuli, it was not included when calculating the syncopation index. C-scores – a measure of counter-evidence to the metre – (Povel and Essens, 1985) were also calculated for each rhythm and were consistent with the syncopation index within each level of complexity (see SFig. 2A and 2B).

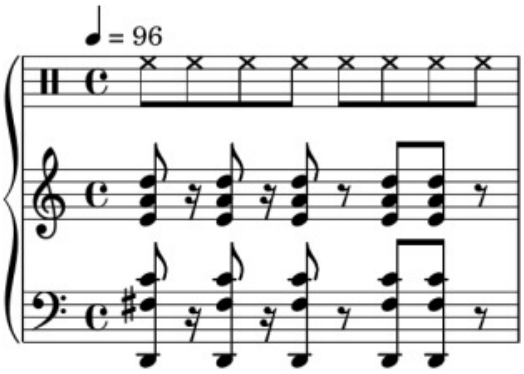

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Fig. 1. Example of a stimulus with medium levels of rhythmic and harmonic complexity.

All chords were in the key of D major and included six notes spanning four octaves (D2 to D#5; see Fig. 1 for musical notation of a medium complexity chord and Table S1 for a list of notes and corresponding frequencies for all chords). In musical terms, the medium complexity chords consisted of four-note chords with extensions. High complexity chords included a flat ninth interval between chord note and extension which is considered highly dissonant, when not specifically occurring as a flat 9th on a major 7th chord, according to contemporary harmonic theory (Freeman and Pease, 1989; Levine, 2011; Nettles and Ulanowsky, 1987). In lay terms, the high complexity chords contained notes with frequencies, or multiples of frequencies, that were very close to each other, thus creating an unpleasant sense of roughness or dissonance, while the medium complexity chords did not. Harmonic complexity was quantified using measures of peak roughness and inharmonicity, calculated using the MIRtoolbox version 1.6.1 (Lartillot et al., 2007; see SFig. 1D and 1C;).

2.3. Procedure

Before arriving for the study, participants filled out a questionnaire about their musical background and demographic information. Upon arrival, participants were familiarized with the stimuli and rating task with four familiarization trials using stimuli that were not included in the main study. There were two sessions during which participants listened to and rated all 36 stimuli, one inside the fMRI scanner

and one outside the scanner. In order to avoid having ratings of wanting to move and pleasure influence each other, participants rated wanting to move in the scanner then pleasure and beat strength outside of the scanner, always in this order. Ratings of beat strength were collected in order to substantiate the rhythmic complexity manipulation and to investigate the association between the sensation of groove and perception of beat strength. In the scanning session, participants underwent three fMRI runs, each lasting around 11 min, during which they listened to all 36 stimuli in a pseudo-random order. A randomly selected subset of 12 stimuli were rated in each scanning run so that all 36 stimuli were rated over the three runs. Rating trials were randomly distributed within each run and participants were not aware that a given sequence would be rated until after it was presented, thus avoiding rating-specific activations. Participants selected their rating on a five-point visual scale by pressing two buttons on a button box to move a cursor right or left along the rating scale. Participants had 7 s to make their rating and non-rated trials had inter-stimulus intervals of five, 7.5, or 10 s. Participants were instructed to look at a fixation cross while sequences were presented.

In order to reduce the effect of scanner noise, stimuli were presented with noise reduction headphones (Opto-Active, OptoAcoustics, Mazor, Israel, http://www.optoacoustics.com/me dical/optoactive/features). In addition, participants wore earplugs inside the headphones. In order to compensate for the low-pass filter effect of the earplugs, the stimuli were compared with and without earplugs and then altered so that they subjectively matched. This resulted in a 10–20 dB increase for frequencies greater than 1500 Hz. This adjustment was identical for all stimuli and participants.

After the scanning, participants listened to the stimuli again while seated at a computer. After each sequence participants had 10 s to rate the degree of pleasure they experienced and the beat strength of the sequence, both on a five-point visual scale,

using a computer mouse to select their rating.

2.4. Behavioural data analysis

Correlations between rating types were tested on participants' averaged ratings (one value per participant). Confidence intervals around correlation coefficients were calculated via bootstrapping with 5000 iterations. Analysis of the effects of rhythmic and harmonic complexity and group on ratings of pleasure, wanting to move, and beat strength were conducted on trial-level ratings using linear mixed effects regression with the lme4 package (Bates et al., 2014) in R (version 3.4.1, R core team, 2017). A linear mixed effects approach was used to account for inter-individual differences in ratings and in the effects of rhythmic and harmonic complexity as well as differences in effects across the three rhythms and chords (referred to as items) within each level of complexity. Starting with the maximal random structure, including by-participant and by-item random slopes and intercepts, this structure was then reduced to the optimal structure that could be supported by the data following the steps of Bates et al. (2015) and using their RePsychLing package. This led to by-participant random slopes and intercepts for rhythmic and harmonic complexity in all three models and by-item random intercepts for the models with wanting to move and beat ratings as outcome variables.

For the effects of interest, a forward hierarchical approach was used whereby regressors were added incrementally to an intercept-only model, then tested for increases in fit using the likelihood ratio test. Regressors that significantly contributed to model fit were included in a final model (fit with restricted maximum likelihood criterion) which was used to get parameter estimates of these regressors. For interactions, estimates of means and mean differences were calculated using emmeans (Lenth et al., 2018). Confidence intervals around the parameter estimates were calculated via parametric bootstrapping with 5000 iterations. Diagnostic plots of the residuals from all models were inspected for violations of the

assumptions of normality and homoscedasticity. No violations were detected.

2.5. MRI data acquisition

Scanning took place at Aarhus University Hospital on a 3T Siemens TIM Trio scanner with a 32-channel coil. Each participant underwent three runs of whole-brain echo-planar imaging (EPI) using a multi-echo sequence which involved acquiring two whole brain volumes at two different echo times (TE1 = 12.4 ms, TE2 = 27.92 ms) per repetition time (TR = 2000 ms and voxel size = 2.35 × 2.53 × 2.50 mm, number of slices = 54, flip angle = 78°). Using the multi-echo sequence reduces signal drop out in regions near sinuses such as the orbitofrontal cortex. The two EPI images within each TR were combined using a signal-to-noise ratio weighted average. This resulted in 326 images per run, with a total of 978 images per participant. T1 structural images were collected for each participant at the start of each session (TR = 2420 ms, TE = 3.7 ms, voxel size = 1 mm iso, flip angle = 9°).

2.6. MRI preprocessing and statistical analysis

Statistical Parametric Mapping software (SPM12 Wellcome Trust Centre for Neuroimaging, University College London; www.fil.ion.ucl.ac.uk/spm/) was used for preprocessing and statistical analysis. Standard preprocessing steps were followed, including slice timing correction, unwarping, motion correction, coregistration to an MNI template, segmentation, spatial normalization, and spatial smoothing with an 8 mm FWHM kernel.

First-level analysis used the general linear model with four condition regressors corresponding to the four types of stimuli (Mr-Mh, Mr-Hh, Hr-Mh, Hr-Hh) as well as twenty-four regressors accounting for motion parameters, and an additional regressor accounting for rating responses which were modeled as events time-locked to button presses. Silent inter-stimulus intervals were unmodeled, thus acting as an implicit baseline.

All regressors were then convolved with a canonical hemodynamic response function. Four contrast images were calculated per participant, corresponding to the four stimuli conditions. These were then entered into a second level analysis where group-level contrasts for each main effect and interaction were generated. All results are reported at a false discovery rate (FDR; peak-level) corrected $p < .05$. In a mixed design, SPM uses the same error term and degrees of freedom for main effects of both within and between-subject factors (Chen et al., 2014, McLaren et al., 2011). Therefore, a confirmatory analysis was implemented in GLM Flex (http://mrtools.mgh.harvard.edu/index.php/GLM_Flex) with the same contrasts and FDR correction (see Tables S2–S4 for results).

2.7. Region of interest analyses

Parameter estimates (betas) for each participant, for each condition were extracted from the putamen and caudate (left and right combined) as well as the left and right nucleus accumbens using Marsbar (Brett et al., 2002; http://marsbar.sourceforge.net/) with anatomical masks from a probabilistic atlas (Hammers et al., 2003). Effects of rhythmic and harmonic complexity and musical training were then assessed using the same approach as the analysis of the ratings. Only by-participant random effects were included since parameter estimates were extracted from group level contrast images which did not contain item (i.e., trial) level activations.

An additional analysis was implemented to investigate the relation between subjective ratings and ROI activity. This analysis also used hierarchical linear mixed effects regression, with parameter estimates from the ROIs as outcome measures, and group, beat strength ratings, pleasure ratings, and wanting to move ratings, as well as interactions between group and the three types of ratings, as predictors. As in the above analysis, only by-participant random effects were included. In order to assess the degree of overlap in variance accounted for by

pleasure and wanting to move ratings, and whether they accounted for variance over and above beat strength ratings and group differences, the hierarchical regression was implemented with two different orders: 1. Group, beat strength ratings, pleasure ratings, and wanting to move ratings, and 2. Group, beat strength ratings, wanting to move ratings, and pleasure ratings. The interactions between group and the ratings were entered after the main effects and followed the same orders. In addition to the final models including only the significant predictors from each hierarchical analysis, models with only pleasure ratings, only wanting to move ratings, and both together as predictors, were assessed.

Based on the findings of the whole brain analysis, a post hoc analysis was implemented to investigate the effect of rhythmic and harmonic complexity as well as the three ratings types on mOFC activity. The mOFC ROI was generated from the any effect whole brain F-contrast (thresholded at $p < 0.05$, FDR) and included two clusters on the left with peaks at $x = -18$, $y = 28$, $z = -18$ and $x = -14$, $y = 42$, $z = -20$ and one cluster on the right with two peaks at $x = 24$, $y = 32$, $z = -12$, and $x = 26$, $y = 32$, $z = -22$. The parameter estimates from this ROI were submitted to two analyses identical to those carried out on the BG ROIs.

The subjective ratings, background data, relevant t-maps, extracted ROI activations that support these findings, as well as the python code for generating stimuli orders, presenting stimuli, and recording responses, are available in the Open Science Framework with identifier link: https://doi.org/10.17605/osf.io/z2sy9.

3. Results

3.1. Behavioural results

All three types of ratings were strongly correlated yet independent enough to be analyzed separately: Pleasure and wanting to move ratings ($r = 0.62$, 95% CI[0.36, 0.81]);

pleasure and beat strength ratings (r = 0.55, 95% CI[0.27, 0.77]); Wanting to move and beat strength ratings (r = 0.42, 95% CI[0.19, 0.61]).

For both musicians and non-musicians, pleasure ratings decreased as rhythmic and harmonic complexity increased (Fig. 2A). However, a significant interaction between rhythmic and harmonic complexity ($\chi_2(1)$ = 8.98, p < .003) showed that the difference in ratings between Mr-Mh and Mr-Hh (mean difference (MD) = 0.696) was greater than the difference between Hr-Mh and Hr-Hh (MD = 0.440; b = 0.250, 95% CI[0.090, 0.409]). This suggests that medium complexity chords increased pleasure to a greater degree when combined with medium complexity rhythms compared to high complexity rhythms. The rhythm by group interaction improved model fit ($\chi_2(1)$ = 4.69, p = .030) and showed that the difference in ratings between medium and high complexity was greater for non-musicians (MD = 1.53) than musicians (MD = 1.17; b = −0.364, 95% CI[-0.679, −0.035]).

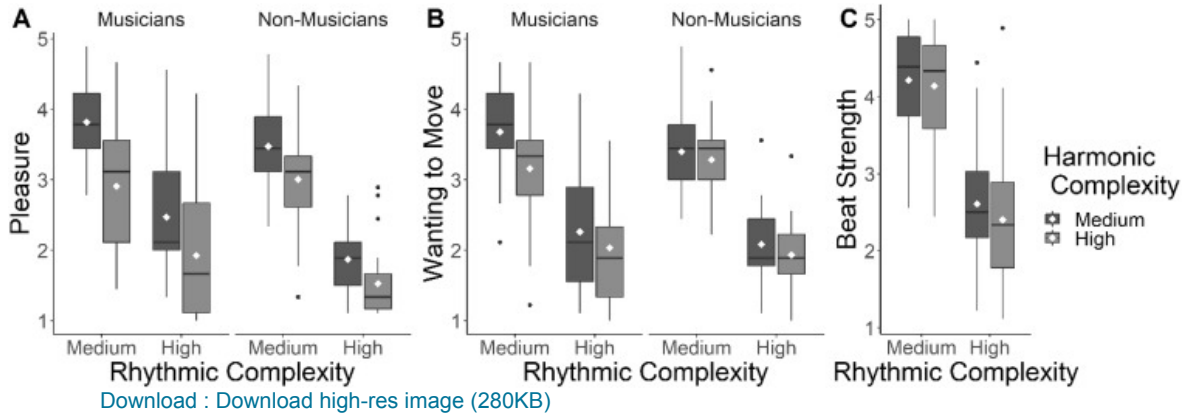

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Fig. 2. Subjective ratings as a function of rhythmic complexity, harmonic complexity and group. **A.** Pleasure ratings. **B.** Wanting to move ratings. **C.** Ratings of beat strength. Center line, median; white dots, means; box limits, upper and lower quartiles; whiskers, 1.5x interquartile range; black dots, outliers.

For wanting to move ratings, there was a three-way interaction with rhythm, harmony, and group ($\chi_2(1)$ = 5.84, p = .016; Fig. 2B). Musicians showed a greater difference in ratings between Mr-Mh and Mr-Hh (MD = 0.521) compared to Hr-Mh and Hr-Hh (MD = 0.226) whereas for non-musicians, the

differences between Mr-Mh and Mr-Hh (MD = 0.116) and Hr-Mh and Hr-Hh (MD = 0.151) were similarly small (b = 0.331, 95% CI[0.062, 0.601]). This suggests that musicians' wanting to move ratings were increased by the combination of medium complexity rhythms and chords whereas non-musicians' ratings were increased by medium complexity rhythms alone.

For beat strength, the main effect of rhythmic complexity significantly improved model fit ($\chi_2(1) = 74.83$, $p < .001$), with medium complexity rhythms rated as having a stronger beat than high complexity rhythms (b = 1.672, 95% CI[1.408, 1.933]). The rhythm by harmony interaction also improved model fit ($\chi_2(1) = 4.08$, $p = .043$) showing that Hr-Mh were rated as having higher beat strength than Hr-Hh (MD = 0.207), whereas Mr-Mh and Mr-Hh were rated more similarly (MD = 0.077; b = −0.130, 95% CI[-0.254, 0.002]; Fig. 2C). This suggests that high complexity rhythms combined with medium complexity chords are rated as having higher beat strength than high complexity rhythms with high complexity chords. However, the confidence interval contains zero suggesting that this effect may be unstable. There was no significant main effect of group nor a significant interaction between group and rhythmic and/or harmonic complexity.

3.2. Whole-brain fMRI results

Whole-brain contrast images were used to assess the effects of rhythm, harmony, and musical training (group). Contrasting medium versus high complexity rhythms (medium > high complexity) revealed activations in the bilateral BG including the putamen, caudate, and pallidum, with activation in the left BG bordering the NAcc. This contrast also revealed activation in a network of cortical regions associated with beat perception including the left SMA (including pre-SMA), bilateral dorsal premotor regions, and bilateral parietal regions (see Table 2 and Fig. 3). In addition, this contrast revealed significant activation in the left prefrontal cortex, left mOFC, the bilateral inferior temporal cortex, and crus 1 in the

right cerebellum. The opposite contrast (high > medium complexity rhythms) revealed no significant activations. Contrasting musicians versus non-musicians (musicians > non-musicians; averaging over all stimuli conditions) revealed activations in the bilateral caudate, bilateral motor cortex (extending into dorsal premotor cortices), bilateral SMA, right prefrontal cortex, right Heschl's gyrus, and left posterior superior temporal gyrus (see Table 3 and Fig. 4). There were no significant activations in the reverse contrast (non-musicians > musicians), nor activations related to harmonic complexity, nor interactions between rhythmic and harmonic complexity or group.

Table 2. Stereotaxic Locations of Peak Voxels in the Medium > High Rhythmic Complexity Contrast. Peak activations thresholded at $p < 0.05$, FDR corrected at the whole-brain level.

Brain region	Cluster size	t(208)	*p*FDR	x	y	z
L putamen	345	5.53	0.004	−14	10	−2
L thalamus		3.61	0.026	−2	−2	8
R putamen	344	5.32	0.004	22	4	8
L inferior parietal lobule	681	4.72	0.007	−42	−48	44
		4.57	0.008	−28	−58	40
		4.35	0.01	−36	−54	40
L SMA	321	4.57	0.008	−6	20	48
		4.31	0.01	−4	12	52
L inferior temporal gyrus	153	4.53	0.008	−58	−40	−18
R angular gyrus	557	4.34	0.01	38	−58	50
R superior parietal lobule		4.32	0.01	34	−66	56
R angular gyrus		4.16	0.011	36	−50	38

L superior frontal gyrus	59	4.32	0.01	−24	14	68
L SMA	210	4.27	0.01	−8	−10	60
R SMA		3.64	0.025	8	−4	68
R middle frontal gyrus	95	4.2	0.011	34	6	52
R inferior temporal	50	3.97	0.015	58	−36	−16
L cerebellum, Crus1	74	3.93	0.015	−14	−92	−22
L inferior frontal pars triangularis	272	3.87	0.017	−40	26	28
L middle frontal gyrus		3.81	0.019	−38	36	16
R cerebellum, Crus 2	22	3.71	0.022	38	−68	−46
R pons	1	3.57	0.028	6	−20	−44
Calcarine sulcus	18	3.54	0.029	0	−82	−12
L superior frontal gyrus	8	3.51	0.03	−20	64	0
L middle frontal gyrus	13	3.47	0.032	−28	0	50
L superior parietal lobule	16	3.46	0.032	−32	−60	62
L medial orbital gyrus	18	3.46	0.033	−14	26	−22
L anterior orbital gyrus		3.36	0.039	−22	24	−22
L anterior cingulum	3	3.41	0.036	−12	32	28
L precentral gyrus	8	3.4	0.036	−16	−18	72
R mid cingulum	21	3.34	0.039	4	−4	30
L precentral gyrus	31	3.34	0.04	−46	8	32
R cerebellum, Crus 2	5	3.33	0.04	12	−88	−28

L frontal superior gyrus	1	3.27	0.044	−16	66	2
R inferior temporal	2	3.27	0.044	42	−50	−8
L precentral gyrus	3	3.26	0.045	−36	6	46
L frontal operculum	1	3.21	0.048	−46	14	2

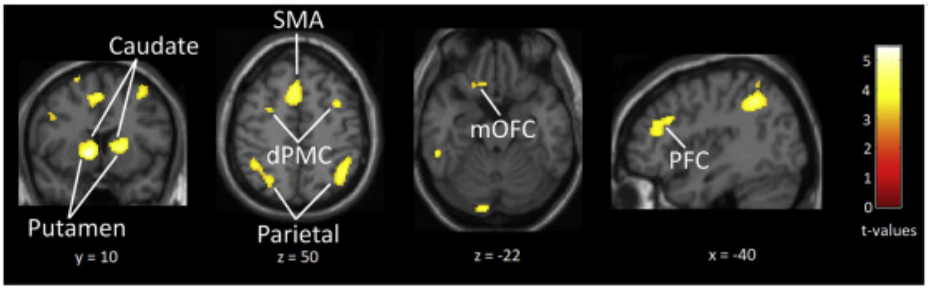

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Fig. 3. Results of the medium > high rhythmic complexity contrast. dPMC, dorsal premotor cortex; mOFC, medial orbitofrontal cortex; PFC, prefrontal cortex; SMA, supplementary motor area. Images are thresholded at $p < 0.05$, FDR corrected at the whole-brain level.

Table 3. Stereotaxic Locations of Peak Voxels in the Musicians > Non-Musicians Contrast. Peak activations thresholded at $p < 0.05$, FDR corrected at the whole-brain level.

Brain region	Cluster size	t(208)	*p*FDR	x	y	z
L precentral gyrus	162	6.1	0	−46	−4	54
White matter	89	4.84	0.004	−38	−42	20
White matter		4.44	0.015	−40	−44	12
R precentral gyrus	105	4.33	0.018	46	−6	48
L SMA	101	4.24	0.023	−2	2	64
R inferior frontal pars triangularis	63	4.19	0.024	44	18	24
R Heschl's gyrus	8	4.16	0.025	56	−8	6
L caudate	55	4.04	0.031	−4	12	4
L superior temporal gyrus	43	4.01	0.032	−58	−48	18
White matter	15	3.98	0.033	22	−12	32
R supramarginal gyrus	3	3.73	0.045	56	−36	26

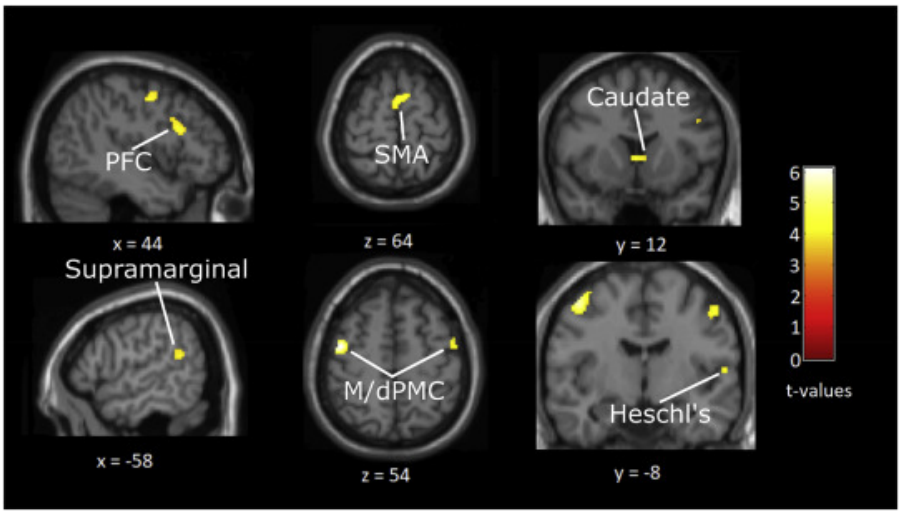

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Fig. 4. Results of the musician > non-musician contrast. M/dPMC, motor/dorsal premotor cortex; PFC, prefrontal cortex; SMA, supplementary motor area. Images are thresholded at $p < 0.05$, FDR corrected at the whole-brain level.

3.3. ROI results

Activity in the right NAcc showed a rhythm by harmony interaction ($\chi_2(1) = 6.50$, $p = .011$). The difference between activation for Mr-Mh versus Mr-Hh (MD = 0.132) was greater than Hr-Mh versus Hr-Hh (MD = −0.063; $b = 0.195$, 95% CI[0.048, 0.343]; Fig. 5B) showing that the largest activation was for stimuli with medium complexity rhythms combined with medium complexity chords. Activity in the left NAcc showed a main effect of rhythmic complexity ($\chi_2(1) = 3.99$, $p = .046$) with greater activation for medium compared to high complexity rhythms ($b = 0.074$, 95% CI[0.001, 0.148]; Fig. 5C). Activity in the caudate showed main effects for both rhythmic complexity ($\chi_2(1) = 12.43$, $p < .001$) and group ($\chi_2(1) = 5.48$, $p = .019$), with greater activation for medium compared to high complexity rhythms ($b = 0.083$, 95% CI[0.038, 0.129]; Fig. 5D) and greater activation in musicians compared to non-musicians ($b = 0.184$, 95% CI[0.030, 0.337]). Activity in the putamen also showed a main effect of rhythmic complexity ($\chi_2(1) = 5.93$, $p = .015$), with greater activation for medium compared to high complexity rhythms ($b = 0.073$, 95% CI[0.015, 0.129]; Fig. 5E). In a post-hoc analysis, activity in the mOFC also showed a main effect of rhythmic complexity ($\chi_2(1) = 6.67$, $p = .01$), with greater

activation for medium compared to high complexity rhythms (b = 0.063, 95% CI[0.015, 0.111]).

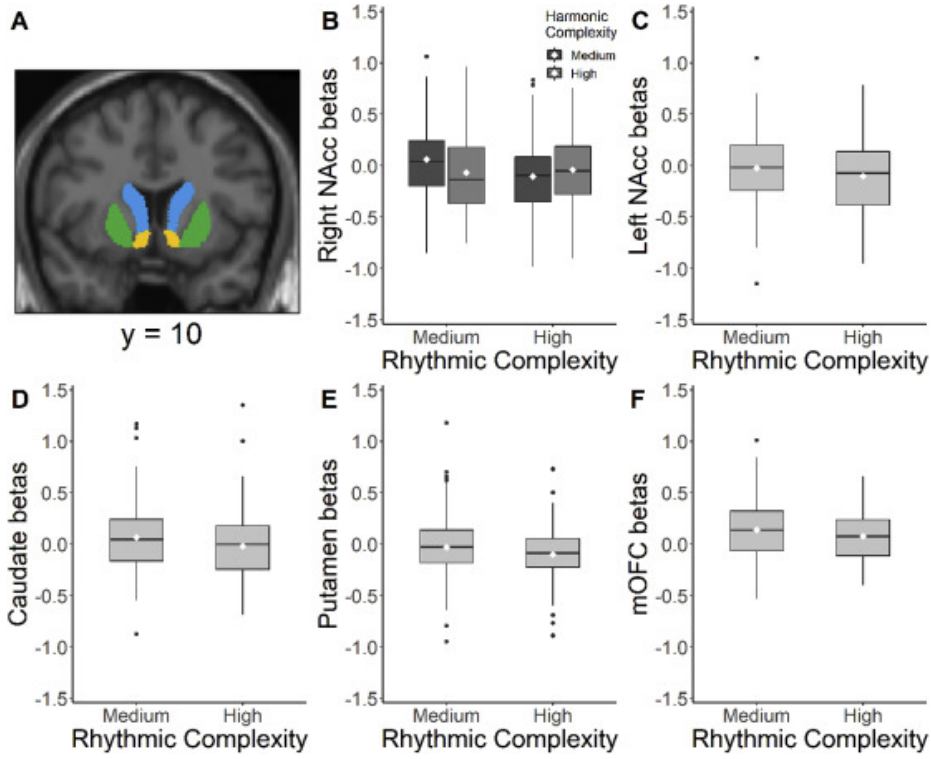

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Fig. 5. Results of ROI analysis. **A.** Coronal view of a single subject MNI template showing BG masks from probabilistic anatomical atlas used in region of interest analyses (Hammers et al., 2003). Blue, caudate; Green, putamen; Orange, nucleus accumbens. **B.** Right nucleus accumbens activation as a function of rhythmic and harmonic complexity. **C.** Left nucleus accumbens activation as a function rhythmic complexity. **D.** Caudate activation as a function of rhythmic complexity. **E.** Putamen activation as a function of rhythmic complexity. **F.** Medial orbitofrontal cortex activation as a function of rhythmic complexity. NAcc, nucleus accumbens; mOFC, medial orbitofrontal. Center line, median; white dots, means; box limits, upper and lower quartiles; whiskers, 1.5x interquartile range; black dots, outliers.

In order to assess the overlap in variance accounted for in the ROI activations by pleasure and wanting to move ratings, the hierarchical regression was implemented twice per ROI, once with pleasure added to the model first and once with wanting to move ratings added first (see Table 4 for results). In addition, final models with both the significant predictors from the hierarchical analyses as well as models with both wanting to move and pleasure as predictors, both alone and together, were assessed (see Table 5 for results and Fig. 6 for summary).

Table 4. Results of Hierarchical Analysis Testing the Association between ROI Activations and Subjective Ratings.

Region	Order	Predictor	$\chi_2(1)$	*p* value
R NAcc				
		Group	2.165	0.141
		Beat	0.868	0.352
	Pleasure First	Pleasure	4.501	0.034
		Move	0.084	0.772
	Move first	Move	2.534	0.111
		Pleasure	2.050	0.152
L NAcc				
		Group	0.487	0.485
		Beat	2.649	0.104
	Pleasure First	Pleasure	4.172	0.041
		Move	1.751	0.186
	Move first	Move	5.389	0.020
		Pleasure	0.534	0.465
Caudate				
		Group	5.481	0.019
		Beat	4.956	0.026
	Pleasure First	Pleasure	2.812	0.094
		Move	3.636	0.057
	Move first	Move	6.448	0.011
		Pleasure	0.000	0.984
Putamen				
		Group	0.863	0.353
		Beat	1.607	0.205
	Pleasure First	Pleasure	3.499	0.061
		Move	3.913	0.048

		Group:beat	9.922	0.002
	Move first	Move	7.401	0.007
		Pleasure	0.011	0.917
mOFC				
		Group	2.510	0.113
		Beat	3.329	0.068
	Pleasure First	Pleasure	0.630	0.427
		Move	4.414	0.036
	Move first	Move	4.499	0.034
		Pleasure	0.546	0.460

Beat, beat strength ratings; Move, wanting to move ratings.

Pleasure, pleasure ratings; NAcc, nucleus accumbens.

mOFC, medial orbitofrontal cortex.

Table 5. Results of Final Models Testing the Association between ROI Activations and Subjective Ratings.

Region	Model	Predictor	β	95% CI
R NAcc				
	Pleasure		0.047	[0.004, 0.089]
	Move		0.042	[-0.004, 0.090]
	Pleasure and Move	Pleasure	0.055	[-0.026, 0.137]
		Move	−0.010	[-0.104, 0.082]
L NAcc				

Pleasure		0.053	[0.015, 0.092]
Move		0.062	[0.018, 0.107]
Pleasure and Move	Pleasure	0.021	[-0.053, 0.094]
	Move	0.042	[-0.040, 0.123]
Caudate			
Group and Beat	Group	0.182	[0.035, 0.335]
	Beat	0.026	[0.003, 0.049]
Group, Beat, and Pleasure	Pleasure	0.035	[-0.006, 0.075]
Group, Beat, and Move	Move	0.064	[0.014, 0.113]
Group, Beat, Pleasure, and Move	Pleasure	−0.001	[-0.056, 0.053]
	Move	0.064	[-0.000, 0.132]
Putamen			
Group:Beat		−0.073	[-0.120, −0.026]
Group:Beat, and Pleasure	Pleasure	0.022	[-0.020, 0.063]
Group:Beat, and Move	Move	0.061	[0.013, 0.109]
Group:Beat, Pleasure, and Move	Pleasure	−0.023	[-0.080, 0.031]
	Move	0.079	[0.014, 0.145]
mOFC			

Pleasure		0.028	[0.000, 0.057]
Move		0.045	[0.016, 0.077]
Pleasure and Move	Pleasure	−0.015	[-0.067, 0.036]
	Move	0.060	[-0.000, 0.119]

Beat, beat strength ratings; Move, wanting to move ratings.

Pleasure, pleasure ratings; NAcc, nucleus accumbens.

mOFC, medial orbitofrontal cortex. Group:Beat, a group by beat

strength ratings interaction from models that also includes the main effect of each.

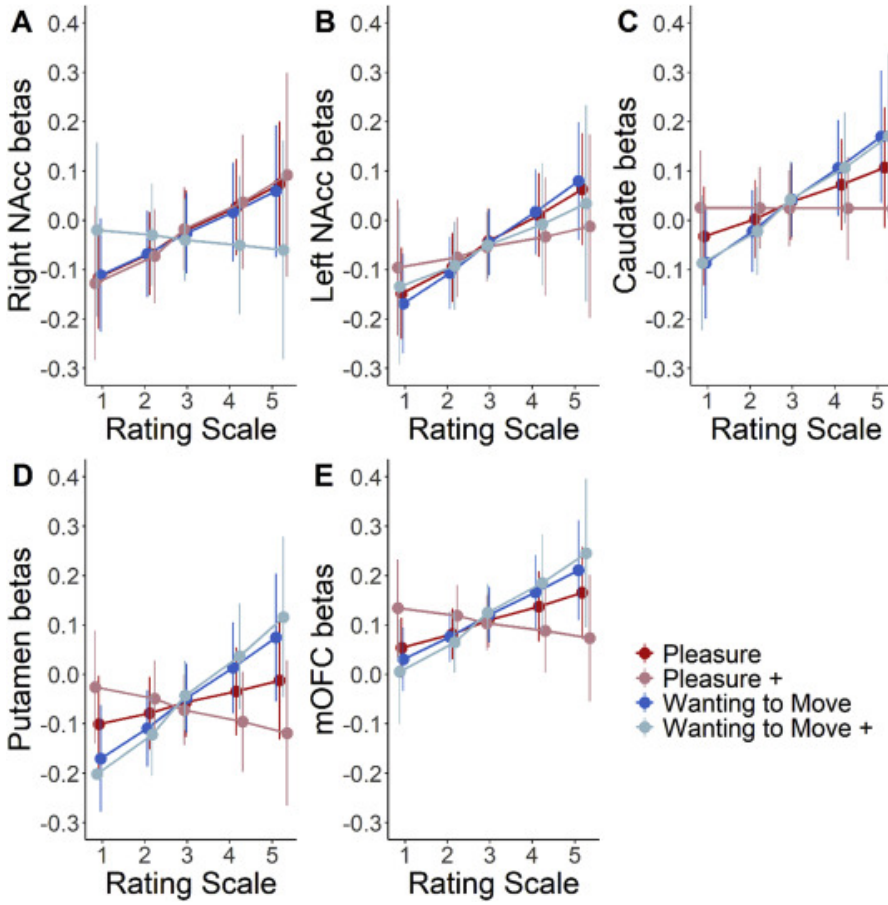

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Fig. 6. Estimated means from regression models testing the effects of pleasure and wanting to move ratings on activation in the regions of interest. Pleasure + denotes models that also include wanting to move ratings and Wanting to Move + denotes models that also include pleasure ratings. Points on the graphs represent estimated mean activations for each rating on the five-point scale of the indicated rating type, while holding the other effects constant at their means. **A.** Right nucleus accumbens. Pleasure and Wanting to Move denote estimated means from models with only those predictors. **B.** Left nucleus accumbens. The models are identical to those in A. **C.** Caudate. All models also include group and beat strength ratings as predictors. **D.** Putamen. All models also include group and beat strength ratings as predictors, as well as an interaction between the two. **E.** Medial orbitofrontal cortex. The models are identical to those in A. NAcc, nucleus accumbens; mOFC, medial orbitofrontal cortex.

Analyses on the right NAcc activations showed that pleasure and wanting to move ratings accounted for overlapping variance, but only pleasure ratings accounted for variance over and above that of beat strength ratings. For the left NAcc activations, both pleasure and wanting to move ratings accounted for variance over and above beat strength ratings, but the variance they accounted for was strongly overlapping. For activity in the caudate, wanting to move but not pleasure ratings, accounted for variance over and above beat strength ratings. A near-significant trend showed that wanting to move ratings accounted for marginally unique variance compared to

pleasure ratings. Analyses on the putamen activations showed that wanting to move ratings accounted for unique variance over and above that accounted for by both beat strength and pleasure ratings. In addition, there was an interaction between group by beat strength ratings, however, due to overlapping variance accounted for, the nature of this interaction depended on the inclusion of wanting to move ratings. Finally, in the mOFC, results showed that wanting to move ratings accounted for variance over and above pleasure ratings. In the final models, wanting to move ratings accounted for unique variance, however, this affect only approached significance.

4. Discussion

In this study we set out to understand the brain networks involved in the sensation of groove. Consistent with previous findings, participants experienced a stronger sensation of groove for medium compared to high levels of both rhythmic and harmonic complexity, with higher ratings of pleasure and wanting to move (Matthews et al., 2019). This was coupled with greater activity for medium complexity rhythms in reward-related regions including the NAcc, caudate, and mOFC, and in regions associated with beat-based timing including the putamen, SMA, as well as prefrontal and parietal cortices. In addition, in both the left and right NAcc, pleasure and wanting to move ratings predicted activity to a similar degree, largely accounting for the same variance. In the mOFC, there was overlap in variance accounted for by wanting to move and pleasure, however, wanting to move was a stronger predictor. In the putamen, wanting to move ratings accounted for variance over and above that accounted for by both pleasure and beat strength ratings. In the caudate, wanting to move ratings and beat strength ratings accounted for overlapping variance. Finally, musicians showed overall greater activity in regions associated with beat perception.

Together, these findings suggest that the sensation of groove is driven by a combination of motor and reward regions in the

brain. We interpret these results in the context of rhythmic expectations, suggesting that the generation of these expectations based on a regular beat, and their violation via syncopations, are core drivers of groove (Matthews et al., 2019; Vuust and Witek, 2014). Based on this formulation, we propose a theoretical model of the brain mechanisms underlying groove that is centered on the cortico-striatal circuits thought to underlie predictive timing and reward processing.

4.1. Medium complexity rhythms drive the sensation of groove

Behavioural results showed that medium complexity rhythms led to higher ratings of pleasure, wanting to move, and beat strength. Only the medium and high complexity conditions were included in order to maximize the number of trials per condition. Therefore, we could not confirm an inverted U-shaped pattern of ratings here. However, ratings for the medium and high complexity rhythms are consistent with those obtained in our previous study which included the low complexity condition (Matthews et al., 2019). Therefore, the current results provide further evidence that medium complexity rhythms strongly contribute to the sensation of groove.

Consistent with previous results, medium complexity chords in combination with medium complexity rhythms increased pleasure ratings, providing further evidence that harmony enhances the affective component of groove (Matthews et al., 2019). Intriguingly, ratings of beat strength were also enhanced by medium complexity chords, supporting previous work showing that beat and metre perception are not driven by rhythmic factors alone (Dawe et al., 1993; Hannon et al., 2004). Finally, for musicians, the combination of medium complexity rhythms and chords enhanced the desire to move, suggesting that for those with musical training, the sensation of groove is more affected by non-rhythmic factors.

4.2. The sensation of groove involves reward regions of the brain

fMRI results showed that medium complexity rhythms were associated with greater activity in the left NAcc and left mOFC. Converging evidence from neuroimaging studies suggests that the NAcc and mOFC are important for the experience of music-derived pleasure (Koelsch, 2014; Martinez-Molina et al., 2019; Martínez-Molina et al., 2016; Salimpoor et al., 2013). Here, activity in both left and right NAcc also showed a positive association with both pleasure and wanting to move ratings, suggesting an association with groove overall rather than the pleasure component alone. One explanation may be that the NAcc is not only involved in the experience of music-derived pleasure, but also in the processing of expectations that can lead to such pleasure (Gebauer et al., 2012; Koelsch, 2014; Salimpoor et al., 2015). For example, NAcc activation has recently been associated with musical uncertainty (Cheung et al., 2019) and musical surprise (Shany et al., 2019), and has also been shown to track reward prediction errors associated with harmonic violations (Gold et al., 2019). In the current study, the right NAcc showed greater activation in response to the combination of medium complexity rhythms and chords, which was the condition that elicited the highest pleasure and wanting to move ratings. Interestingly, this was the only region to show an effect of harmonic complexity, which might relate to the right-dominance of regions involved in tonal processing (Zatorre et al., 2002).

Activity in the mOFC has been associated with assigning affective value to stimuli, including music (Zatorre and Salimpoor, 2013). However, in the current results mOFC activity showed a stronger association with wanting to move ratings than with pleasure ratings. A more recent hypothesis suggests that OFC involvement in value assignment is contingent on whether this process involves mental simulation of behavioural outcomes (Stalnaker et al., 2015). This is consistent with the current results as wanting to move ratings, in contrast to pleasure ratings, may involve action simulation.

Therefore, one possibility is that the NAcc encodes the positive affective state of groove, while the mOFC encodes the association between the music and the desire to move.

4.3. The sensation of groove involves motor regions of the brain

Our results also showed greater activation in bilateral putamen and caudate as well as the SMA (including pre-SMA) and bilateral dorsal premotor cortices for medium complexity rhythms. The putamen and the SMA are part of the cortico-striatal 'motor circuit' (Alexander et al., 1986) and together with the caudate are suggested to be crucial nodes in both the striatal beat-frequency and pacemaker-accumulator models of timing (Coull et al., 2011; Matell and Meck, 2004; Merchant et al., 2013). In addition, recent theories suggest that temporal predictions are generated in the motor system via covert and unconscious action simulation (Arnal, 2012; Patel and Iversen, 2014; Rimmele et al., 2018; Ross et al., 2016; Schubotz, 2007). This is supported by a recent study showing that temporal predictions in the context of regular auditory stimuli are driven by motor signals to the auditory cortex (Morillon and Baillet, 2017). In the context of beat perception, the efferent signals of these covert actions may act as an internal representation of the beat, or 'pacing signal' (Kotz et al., 2016), informing beat-based expectations.

Converging evidence suggest that the putamen, SMA and dorsal premotor cortices are crucial for generating an internal representation of a beat (Araneda et al., 2016; Grahn and Brett, 2007; Grahn and Rowe, 2009; Merchant et al., 2015), with the putamen seeming particularly important (Grahn and Rowe, 2013). Studies with both Parkinson's disease (Grahn and Brett, 2009) and lesion patients (Nozaradan et al., 2017) also support the importance of the BG in beat perception. Furthermore, oscillatory activity in the SMA and putamen has been shown to entrain to frequencies denoting the beat and metre, respectively (Li et al., 2019). However, two recent studies using transcranial magnetic stimulation (TMS) support the role of the dorsal

premotor cortex (Ross et al., 2018a) but not the SMA (Ross et al., 2018b) in beat perception.

Interestingly, the caudate was the only region of interest whose activity showed a main effect of beat strength ratings. However, further analysis revealed strong overlap between the effects of beat strength and wanting to move ratings in this region. Beat strength ratings did show a relation to putamen activity via an interaction with group, the nature of which also depended on the inclusion of wanting to move ratings in the model. Together these results provide further evidence that beat perception and motor activation are strongly linked, both in terms of subjective experience and neural underpinnings.

4.4. The sensation of groove involves frontoparietal networks

Medium complexity rhythms also elicited increased activation in bilateral parietal (with peaks in inferior and superior parietal lobules) and left prefrontal cortical regions. Parietal and prefrontal regions are components of both the dorsal auditory (Hickok and Poeppel, 2004; Rauschecker, 2011) and the fronto-parietal networks (Ptak et al., 2017), which are thought to underlie the motor representations of stimuli allowing for the processing of sensory input that evolves over time (Ptak et al., 2017; Rauschecker, 2011). These regions have also been implicated in the cognitive aspects of temporal and rhythmic processing including temporal attention (Bolger et al., 2014; Coull and Nobre, 2008; Coull et al., 2011; Davranche et al., 2011; Nobre and van Ede, 2017), encoding and retrieval of beat-based time intervals (Konoike et al., 2015, 2012), and rhythmic deviant detection (Lappe et al., 2016, 2013). A recent TMS study showed that down-regulating parietal activity disrupts perception of phase shifts of the beat (Ross et al., 2018b). These results are consistent with the parietal cortices purported role as the interface between motor-driven temporal predictions and sensory input (Rauschecker, 2011; Rimmele et al., 2018).

Prefrontal activity during beat perception has been linked to precision of sensory predictions (Bengtsson et al., 2009) and working memory (Kung et al., 2013), consistent with its role in beat-based timing (Teki et al., 2011). Therefore, the dorsal prefrontal activity seen here may represent the generation of beat-based expectations and monitoring of their outcome. The caudate is strongly connected to prefrontal and parietal regions (Haber, 2016), and both whole-brain and ROI analyses showed greater caudate activation for medium complexity rhythms. A recent study using TMS suggests that a left dorsolateral prefrontal-caudate circuit determines music liking and wanting by coding musical expectancies based on structural properties (Mas-herrero et al., 2018). In the current context, prefrontal and parietal regions, along with the caudate, may generate and update beat-based expectations and compare these expectations to incoming stimuli.

4.5. Musicians show greater activation in regions associated with beat-based timing

Although the overall pattern of activity was similar for both groups, musicians showed greater activity in the caudate, right prefrontal cortex, SMA, primary and premotor cortex and primary and secondary auditory regions, compared to non-musicians, regardless of rhythm complexity. Musicians have shown greater activity in the SMA and premotor cortex (Grahn and Brett, 2007) and greater connectivity between SMA and auditory regions (Grahn and Rowe, 2009) during rhythm perception tasks. Together, these results suggest that musical training leads to greater engagement of regions involved in beat perception as well as stronger auditory-motor associations (Alluri et al., 2017; Zatorre et al., 2007). This is in line with the current behavioural findings, as well as those from a previous study showing that musicians are more sensitive to rhythmic and harmonic manipulations (Matthews et al., 2019), and with results showing greater neural responses to rhythmic deviants (Geiser et al., 2010; Habibi et al., 2014; Vuust et al., 2009).

4.6. A proposed model

We propose a theoretical model integrating the current results with previous work discussed above. According to this model, the putamen, along with the SMA and premotor cortices automatically generate an internal representation of the beat. These regions interact with the caudate, prefrontal, and parietal regions which use this beat representation to inform rhythmic expectations and compare them to incoming stimuli. These regions may also use this beat information to generate higher-level expectations regarding the way music will unfold over longer timescales (Salimpoor et al., 2015). Information from both the putamen and caudate networks may then be passed to the NAcc-mOFC circuit which generates a positive affective response, including both pleasure and the desire to move, and assigns value to both rhythmic and higher-level expectations. Medium complexity rhythms activate these networks as they are regular enough to allow for internal beat generation, but also contain syncopations that challenge this regularity and thus engage expectation processes leading to the pleasurable desire to move. In addition, the repetition of rhythmic patterns, used here in our stimuli and common in groove-based music (Danielsen, 2006), may engage processes involved in higher-level expectations. Furthermore, musical training may strengthen these expectations and the brain networks that support them. Finally, although rhythm appears to be the primary feature influencing groove, other factors, including harmony and familiarity also enhance pleasure (Matthews et al., 2019; Pereira et al., 2011; Senn et al., 2019; van den Bosch et al., 2013).

5. Conclusion

The current study sought to investigate the brain networks underlying the pleasurable desire to move to music, known as the sensation of groove. Medium complexity rhythms led to greater activity in brain regions associated with both motor timing and reward. Subjective ratings of pleasure and wanting to move were associated with activity in BG regions of interest supporting their crucial role, not only in processing rhythmic

complexity, but also in the subjective experience of groove. These results provide novel evidence supporting the formulation of groove as the intersection of motor timing and reward processes. Based on this formulation, we propose a model in which different cortico-striatal networks support the generation and affective valuation of beat-based expectations. Future studies will test the interactions between these networks, leading to a better understanding of how prediction and reward-based mechanisms work together.

Rhythm and Beat Perception in Motor Areas of the Brain Jessica A. Grahn and Matthew Brett Abstract & When we listen to rhythm, we often move spontaneously to the beat. This movement may result from processing of the beat by motor areas. Previous studies have shown that several motor areas respond when attending to rhythms. Here we investigate whether specific motor regions respond to beat in rhythm. We predicted that the basal ganglia and supplementary motor area (SMA) would respond in the presence of a regular beat. To establish what rhythm properties induce a beat, we asked subjects to reproduce different types of rhythmic sequences. Improved reproduction was observed for one rhythm type, which had integer ratio relationships between its intervals and regular perceptual accents. A subsequent functional magnetic resonance imaging study found that these rhythms also elicited higher activity in the basal ganglia and SMA. This finding was consistent across different levels of musical training, although musicians showed activation increases unrelated to rhythm type in the premotor cortex, cerebellum, and SMAs (pre-SMA and SMA). We conclude that, in addition to their role in movement production, the basal ganglia and SMAs may mediate beat perception. & INTRODUCTION In most Western music, people perceive a regular, underlying pulse called the ''beat'' or ''tactus'' (Drake, Penel, & Bigand, 2000). Perception of the beat often causes spontaneous synchronized movement, such as toe tapping or head nodding. The presence of a beat also affects the ability to remember and perform a rhythm. For example, when a rhythm is presented with a beat (the beat occurring as a series of external metronome clicks), reproduction accuracy of the rhythm improves (Patel, Iversen, Chen, & Repp, 2005; Essens & Povel, 1985). The beat is emphasized in musical contexts by nontemporal cues such as pitch, volume, and timbre, yet even rhythms without these cues can induce listeners to ''feel'' a beat internally (Brochard, Abecasis, Potter, Ragot, & Drake, 2003). The beat is somehow conveyed solely by the temporal properties of the rhythm itself. It is still unclear, however, exactly what temporal properties are critical for beat perception to spontaneously occur. One property that may be important for beat perception in rhythm is the presence of simple integer ratio relationships between intervals in a sequence (Sakai et al., 1999; Essens, 1986). For example, a sequence containing intervals of 250, 500, and 1000 msec has a 1:2:4 relationship between its intervals. By using a beat that is the length of the smallest interval, the sequence can be encoded in terms of beats, instead of encoding each individual interval length. In noninteger ratio sequences (e.g., 1:2.4:3.6) beats cannot be used, and thus, sequence reproduction is worse. Subjects may even ''regularize'' noninteger ratio sequences, reproducing them as integer ratios (Collier & Wright, 1995; Essens, 1986). Others

propose that integer ratios are insufficient to induce a beat and that regularly occurring ''perceptual accents'' may also be necessary (Essens & Povel, 1985). Accents cause a particular note to feel more prominent than surrounding notes, and previous work shows that our attention is attracted to accented events (Drake, Jones, & Baruch, 2000; Jones & Pfordresher, 1997; Jones & Boltz, 1989). One common type of accent occurs in music, where louder notes are perceived as more prominent. However, humans perceive a beat in rhythmic patterns even when no volume changes occur. In this case, any perceptual accents that occur are due to the temporal pattern. This is the type of accent investigated in the current experiments: the type of accent that arises solely from the temporal context when all other factors (such as pitch or volume) are held constant. For example, onsets not closely followed by other onsets in time are perceived as accented (Parncutt, 1994), as is the final onset of two or three onsets in a row (Povel & Okkerman, 1981). The latter type of accent is present in the Overture to William Tell (da da dum, da da dum, da da dum dum dum ...) on the ''dum'' of each ''da da dum.'' If perceptual accents occurring at regular MRC Cognition and Brain Sciences Unit, Cambridge, UK temporal intervals are necessary to feel the beat, then D 2007 Massachusetts Institute of Technology Journal of Cognitive Neuroscience 19:5, pp. 893–906 sequences with this property should be reproduced more accurately (Essens, 1995). Perceptual accents have not always been considered in previous research (Sakai et al., 1999). Thus, enhancement in integer ratio sequence performance may be due to some sequences in that condition that also had regular perceptual accents. The role of perceptual accents and integer ratios in rhythm reproduction is examined in our first experiment. Subjects listened to and then reproduced rhythms that contained either integer ratios or noninteger ratios and regular or irregular perceptual accents. A follow-up functional magnetic resonance imaging (fMRI) study used the same rhythms to investigate neural activity during rhythm perception. Perception and production are likely to rely on similar neural mechanisms, as previous behavioral work demonstrates comparable difference thresholds between timing during perception and production tasks (Ivry & Hazeltine, 1995). This behavioral similarity is supported by neuroimaging experiments. Timing, duration perception, and rhythm perception and production tasks consistently activate the same brain areas, including the premotor and supplementary motor areas (SMAs), cerebellum, and basal ganglia (Coull, Vidal, Nazarian, & Macar, 2004; Lewis, Wing, Pope, Praamstra, & Miall, 2004; Pastor, Day, Macaluso, Friston, & Frackowiak, 2004; Dhamala et al., 2003; Ferrandez et al., 2003; Nenadic et al., 2003; Ramnani & Passingham, 2001; Rao, Mayer, & Harrington, 2001; Schubotz & von Cramon, 2001; Penhune, Zatorre, & Evans, 1998). Damage to these areas also impairs timing abilities (Molinari, Leggio, De Martin, Cerasa, & Thaut, 2003; Mangels, Ivry, & Shimizu, 1998; Halsband, Ito, Tanji, & Freund, 1993; Artieda, Pastor, Lacruz, & Obeso, 1992). It is thus reasonably clear that the timing processes that underlie both perception and production involve these areas. However, these brain regions are unlikely to subserve identical timing functions. It has been suggested that one distinction between commonly activated neural structures may be their respective roles in ''automatic'' timing, defined as ''the continuous measurement of predictable subsecond intervals defined by movement,'' and ''cognitively controlled'' timing, defined as the ''measurement of suprasecond intervals not defined by movement and occurring as discrete epochs'' (Lewis & Miall, 2003). Beat perception has characteristics of both automatic and cognitively controlled timing, as the length of the beat humans perceive can span from approximately 200 to 2000 msec (Parncutt, 1994; Warren, 1993), and the beat may or may not be marked by movement. Accordingly, a different distinction may be that certain motor areas are involved in extracting a regular beat from incoming temporal stimuli. The role for motor areas in beat processing is supported by findings of a direct link between movement and beat perception in infants (Phillips-Silver & Trainor, 2005). Thus, the current studies were conducted to determine if certain brain areas responded to perception of a beat (induced by the temporal structure of the rhythms). Beat

perception may require a temporal representation or level of processing that is more complex than that required for the more basic timing of individual intervals. Given that the basal ganglia and SMA are not only involved in attention to time (Coull et al., 2004), but are critical to temporal sequencing (Shima & Tanji, 2000; Brotchie, Iansek, & Horne, 1991) and predictable, internally generated movements (Cunnington, Windischberger, Deecke, & Moser, 2002; Freeman, Cody, & Schady, 1993), we hypothesize that they are the most likely candidate areas for the detection or generation of an internal beat. METHODS Reproduction Experiment Subjects and Stimuli Twenty subjects (9 men, 11 women) took part in the reproduction experiment. Subjects ranged in age from 24 to 40 years, with an average age of 30 years. For each condition, 30 rhythmic sequences were constructed from sets of five, six, or seven intervals. The intervals in the metric rhythms were related by ratios of 1:2:3:4, and the intervals in the nonmetric rhythms were related by ratios of 1:1.4:3.5:4.5. The metric rhythms were of two types: simple and complex. In the metric simple condition the intervals were arranged to induce a perceptual accent at the beginning of each group of four units (see Figure 1). Nothing was added to the sequence to produce the perceptual accents: they arise spontaneously from the temporal Figure 1. Schematic of sample stimuli. Vertical bars indicate interval onset; ''>'' indicates where perceptual accents should be heard (Povel & Okkerman, 1981). Perceptual accents can occur on final interval onsets of consecutive runs of two or three short intervals and on onsets either preceded or followed by a relatively long period of no onsets (such as the first and last onsets of a sequence). 894 Journal of Cognitive Neuroscience Volume 19, Number 5 context, in accordance with the model of Povel and Essens (Essens & Povel, 1985). The perceptual accents were there to induce subjects to hear a regular beat coinciding with the onset of each group of four units. Other work in our laboratory suggests that participants' representation of the beat agree with the model's accent predictions. Pilot data reveal that when participants are asked to listen to rhythmic sequences and decide if a beat is present, a beat is felt 90% of the time for metric simple sequences. Increased finger tap velocity or force on particular taps during reproduction can also indicate where participants feel the beat. When tap velocity was measured during a reproduction task similar to the one outlined here, the velocity was significantly higher for taps coinciding with the perceptual accents at the onset of each group of four units than for the other taps in each sequence (Grahn & Brett, 2005, 2006). In the metric complex condition, the intervals were identical to those in the metric simple condition, but rearranged so as not to be regularly grouped, and therefore had irregular perceptual accents. The nonmetric rhythms had the same interval arrangements as the metric complex rhythms but used the noninteger ratio interval lengths: 1.4 replaced 2, 3.5 replaced 3, and 4.5 replaced 4. For a complete list of sequences, see Table 1. The length of the ''1'' interval was chosen randomly from 220 to 270 msec (in 10-msec steps) on each trial to prevent subjects from using a beat perceived in the previous trial. The rest of the intervals in each sequence were multiples of the 1 interval. For example, with a 1 interval of 250 msec, the sequence 321411 has intervals of length 750 500 250 1000 250 250 (msec). Sine tones (rise/fall times of 8 msec) sounded for the duration of each interval, ending 40 msec before the specified interval length to create a silent gap that demarcated the intervals. The sequences used filled intervals, as piloting indicated performance was similar for empty and filled interval sequences, and filled intervals provide the benefit of attenuation of environmental noise (e.g., that experienced during MRI). In addition, differences in the average psychophysical discrimination threshold between empty and filled auditory intervals are a few milliseconds and thus unlikely to affect perception of sequences composed of the interval lengths used here (Grondin, 1993). One of six pitches (varying from 294 to 587 Hz) was picked at random for each trial and held constant for that trial. The pitch differences between trials helped cue subjects to each new trial. In the first experiment, the task was to reproduce the sequence as accurately as possible. During reproduction, the onset of each reproduced interval is indicated by the subject's tap, and the

reproduced lengths of each interval were measured by the intertap time. We therefore added an additional tone, the length of the 1 interval, to the end of each sequence. Otherwise, without this final onset for subjects to tap, the last reproduced interval's length would not have been measured. Experimental Design Rhythms were presented diotically over headphones. On each trial a rhythm was presented three times, with 1100 msec between presentations. After the third presentation, subjects tapped the rhythm from memory on one key of a computer keyboard. Subjects had 4.5 sec to tap the rhythm before the next one was presented. Subjects practiced four trials, then completed three blocks of 30 trials each. There were 30 trials of each rhythm type (metric simple, metric complex, nonmetric) presented in random order. Data Analysis Performance was evaluated based on the keypresses the subjects reproduced. Trials with the incorrect number of keypresses or incorrect order of intervals were considered errors. Incorrect ordering was defined as any reproduced interval exceeding the length of another reproduced interval that was supposed to be shorter (e.g., a 2 interval exceeding the length of a 3 interval) and vice versa (e.g., a 4 interval shorter than a 1 interval). More stringent criteria (e.g., rejecting any sequence with a reproduced interval that deviated by more than 10% or 20% of the specified interval length) were also used, but led to the same pattern of results between conditions and thus are not presented here. On correct trials, the reproduced ratios were calculated from the mean duration of each reproduced interval length on each trial. Perfect reproduction results in ratios of 2, 3, and 4 for both metric conditions, and 1.4, 3.5, and 4.5 for the nonmetric condition. In order to compare accuracy between conditions, each reproduced ratio was divided by its ideal ratio (the ratio actually presented in the stimulus), so reproduction across the different ratios was normalized to 1 (perfect reproduction). The absolute value of the deviation from 1 was then tested to see if accuracy differed across ratios and conditions. Functional Imaging Experiment Subjects Twenty-seven right-handed subjects participated (19 men, 8 women). Fourteen had musical training (over 5 years of formal musical training and current regular musical activity) and 13 had no musical training (reported no formal musical training or musical activities). They ranged in age from 19 to 38 years, and the average age was 24.5 years. The fMRI participants had not taken part in the previous reproduction experiment. Experimental Design Rhythms were presented diotically over electrostatic headphones (Palmer, Bullock, & Chambers, 1998) inserted into Grahn and Brett 895 sound-attenuating ear defenders. Further attenuation of scanner noise was achieved with insert earplugs rated to attenuate by 30 dB (3M 1100 earplugs, 3M United Kingdom PLC, Bracknell, UK). When wearing earplugs and ear defenders, participants reported no difficulty in hearing the rhythms or focusing on the task. The discrimination task used the same sequences as the reproduction task but required participants to listen to two identical presentations of a rhythm, to which they compared a subsequent third presentation. The third presentation could be the same rhythm or a different rhythm. To indicate whether the third rhythm was same or different, participants pressed one of two buttons with either the right index or middle finger. On 39% of trials the third presentation was different. Each rhythm presentation was separated by 1100 msec. The deviant sequences contained Table 1. Rhythmic Sequences for Each Condition Interval Set Metric Simple Metric Complex Nonmetric 5 Intervals 11334 31413 11343 1 1 3.5 4.5 3.5 41331 33141 3.5 3.5 1 4.5 1 43113 41133 4.5 1 1 3.5 3.5 12234 22413 13242 1 3.5 1.4 4.5 1.4 31422 21324 1.4 1 3.5 1.4 4.5 43122 41232 4.5 1 1.4 3.5 1.4 6 Intervals 111234 112314 124113 1 1.4 4.5 1 1 3.5 211134 214311 1.4 1 4.5 3.5 1 1 211413 321411 3.5 1.4 1 4.5 1 1 411231 421311 4.5 1.4 1 3.5 1 1 112224 112422 122142 1 1.4 1.4 1 4.5 1.4 211224 214221 1.4 1 4.5 1.4 1.4 1 222114 221241 1.4 1.4 1 1.4 4.5 1 422112 412212 4.5 1 1.4 1.4 1 1.4 112233 221331 121233 1 1.4 1 1.4 3.5 3.5 223113 132321 1 3.5 1.4 3.5 1.4 1 311322 231123 1.4 3.5 1 1 1.4 3.5 312213 323211 3.5 1.4 3.5 1.4 1 1 7 Intervals 1111134 1111431 1314111 1 3.5 1 4.5 1 1 1 3141111 1411311 1 4.5 1 1 3.5 1 1 4111131 3114111 3.5 1 1 4.5 1 1 1 1111224 1122114 1112412 1 1 1 1.4 4.5 1 1.4 2211114 2141211 1.4 1 4.5 1 1.4 1 1 4221111

4111221 4.5 1 1 1 1.4 1.4 1 1111233 1123113 1132131 1 1 3.5 1.4 1 3.5 1 2113113 2331111 1.4 3.5 3.5 1111 3121113 3113121 3.5 1 1 3.5 1 1.4 1 1112223 1123122 1132212 1 1 3.5 1.4 1.4 1 1.4 2112231 2123211 1.4 1 1.4 3.5 1.4 1 1 3122112 3221112 3.5 1.4 1.4 1 1 1 1.4 1 = 220–270 msec (in steps of 10 msec), chosen at random for each trial. All other intervals in that sequence are multiplied by length chosen for the 1 interval. 896 Journal of Cognitive Neuroscience Volume 19, Number 5 two temporal changes (as piloting indicated that the presence of two deviants allowed behavioral performance between conditions to be equal, but not at ceiling or floor). One interval in the sequence was divided into two intervals, and two separate intervals were combined into one (e.g., 211314 becomes 223113, 11 ! 2, and 4 ! 13). Thus, the number of intervals and overall sequence length was identical between standard and deviant sequences. Before scanning, participants completed eight practice trials. During scanning, participants completed four consecutive sessions of 38 trials each, approximately 40 min in total. Trials were equally distributed between four types: rest (no sound presented), metric simple, metric complex, or nonmetric rhythms, presented in a pseudorandom order. Participants were instructed not to move any part of their body during the scan (other than to respond). Image Acquisition Participants were scanned on a Bruker MEDSPEC 3-T scanner at the Wolfson Brain Imaging Centre in Cambridge, using a head coil gradient set. Echo-planar imaging (EPI) data were collected with the following parameters: 21 slices, matrix size of 64 64, TE = 37.5 msec, TR = 1.1 sec, FOV = 20 20 cm, flip angle = 65.58. The resulting EPIs had a slice thickness of 4 mm, interslice distance of 1 mm, and in-plane resolution of 3.125 3.125 mm. The EPI acquisition was continuous to prevent periodic silent gaps between TRs from disrupting participants' encoding of the rhythms. Although some studies of auditory cortex have used ''sparse'' imaging in order to reduce the effects of scanner noise on detecting subtle differences in auditory activity, we chose to use standard continuous imaging, as this offered considerably greater power (number of scans) and the stimuli were easily heard over the scanner noise. In addition, motor areas, not auditory areas, were of primary interest. A map of the magnetic field was acquired to correct for distortion to the EPIs resulting from inhomogeneities in the field. High-resolution three-dimensional spoiled gradient recalled (SPGR) at steady-state anatomical images were collected for anatomic localization and coregistration. Image Processing and Statistical Analysis SPM2 was used for preprocessing of the fMRI data and SPM99 for statistical analysis (SPM99, SPM2; Wellcome Department of Cognitive Neurology, London, UK). SPM99 was used to take advantage of previously adapted routines to remove time series artifacts from the data (www.mrc-cbu.cam.ac.uk/Imaging/Common/missing_ time.shtml). Images were slice-timing corrected, with the first slice in each scan used as a reference. They were then realigned spatially (to correct for subject motion) with respect to the first image in the series by using trilinear interpolation. Magnetic field maps were used to undistort the EPI images (Cusack & Papadakis, 2002). The SPGR image was skull-stripped by using the Brain Extraction Tool (BET) (Smith, 2002), then normalized (using affine and smoothly nonlinear transformations) to a brain template in Montreal Neurological Institute (MNI) space. The resulting normalization parameters were then applied to the EPIs and all normalized EPI images were spatially smoothed with an 8-mm full width half maximum Gaussian kernel. For each participant, each session, and each condition (metric simple, metric complex, and nonmetric) the following event types were modeled separately: first presentation; second presentation; third presentation for same trials; third presentation for different trials; button press response. Each event was modeled by using a regressor made from an on–off boxcar convolved with a canonical hemodynamic response function. Six estimated parameters of movement between scans (translation and rotation along x, y, and z axes) were entered as covariates of no interest. Before running the model, the time course of the average brain signal was screened for spikes of high variance. Short periods of high variance are usually associated with brief subject movements as shown in the spatial realignment parameters. The high-variance scans

were removed from the model by using a modified version of the SPM99 modeling routines (www.mrc-cbu.cam.ac.uk/Imaging/Common/ missing_time.shtml). Low-frequency noise was removed with a standard high-pass filter of 120 sec. The results estimated from single subject models were entered into second-level random effects analyses for standard SPM group inference (Penny & Holmes, 2003). All reported peaks passed a whole-brain false detection rate (FDR) threshold (Genovese, Lazar, & Nichols, 2002; Benjamini & Hochberg, 1995) of $p < .05$. A region-of-interest (ROI) analysis was conducted to test the prediction that the basal ganglia and SMA are more active to rhythms that induce a beat, and to elucidate the pattern of activation between conditions in other ROIs. For the basal ganglia, where structure is easily defined by anatomy and relatively invariant across individuals, structural ROIs were used for the pallidum, putamen, and caudate (Tzourio-Mazoyer et al., 2002). For the SMA, dorsal premotor areas (PMds), superior temporal gyri, and cerebellum, functional ROIs were defined from the all rhythms–rest contrast. The SMA activation was predominantly anterior to the anterior commissure, so the SMA ROI should be considered to be largely pre-SMA with some component of SMA proper (Picard & Strick, 1996; Rizzolatti, Luppino, & Matelli, 1996). The ROI analysis was conducted with the software package MarsBar (marsbar.sourceforge.net). For each ROI, a t test was carried out to compare the mean voxel value during trials of each rhythm type, and between each group. Grahn and Brett 897 RESULTS Reproduction Results After hearing a rhythm three times, participants tapped the rhythm back on one key of a computer keyboard. As shown in Figure 2, participants correctly performed metric simple rhythms significantly more often than the metric complex and nonmetric rhythms (metric simple, 74% correct; metric complex, 53% correct; nonmetric, 58% correct). Metric complex and nonmetric rhythms were not significantly different in percent correct performance, as confirmed by a one-way analysis of variance (ANOVA) with Rhythm type (metric simple, metric complex, nonmetric): $F(2,38) = 20.67$, $p < .001$, with Bonferroni-corrected post hoc tests: metric simple versus metric complex: $t(1,19) = 5.47$, $p < .001$; metric simple versus nonmetric: $t(1,19) = 5.24$, $p < .001$; metric complex versus nonmetric: $t(1,19) = 1.38$, $p = .19$. The error types varied widely and could be due to the taxing nature of the reproduction task on working memory. Usually just part of the sequence was reproduced incorrectly. For example, in sequences with several short intervals in a row, participants sometimes reproduced the wrong number of short intervals, but the rest of the intervals were correct. Sometimes just the beginning or the end of a sequence was reproduced incorrectly. Other time intervals were transposed. Occasionally participants only reproduced the beginning or the end of a sequence without attempting the rest of the sequence. Analyses of how accurately participants reproduced the timing of the intervals were conducted on sequences where the overall order of the intervals was correct (see Methods for details). Perfect reproduction would result in ratios of 2:3:4 for the metric conditions, and 1.4:3.5:4.5 for the nonmetric condition. The ratios reproduced by the participants were, in the metric simple condition, 2.08:3.01:3.83 (SE = .04, .06, .10); in the metric complex condition, 2.05:2.84:3.34 (SE = .04, .08, .11); and in the nonmetric condition, 1.41:2.95:3.51 (SE = .04, .09, .12). Overall, in all conditions, participants tended to shorten the longest intervals in a sequence. To determine if the timing accuracy significantly differed between conditions, the absolute value of the deviation of these ratios from perfect performance was tested. Differences between conditions were confirmed by a significant interaction between Rhythm type and Ratio on timing accuracy: $F(4,76) = 4.41$, $p = .003$. Further analyses revealed that accuracy of the longest ratios (the 4 ratio in the metric conditions and the 4.5 ratio in the nonmetric condition) did significantly differ between conditions. The accuracy of the longest ratio in the metric simple condition was significantly better than in the metric complex and nonmetric conditions, which did not significantly differ: metric simple versus metric complex, $t(1,19) = 6.52$, $p < .001$; metric simple versus nonmetric, $t(1,19) = 5.00$, $p < .001$; metric complex versus nonmetric, $t(1,19) = 1.42$, $p = .17$ (Bonferroni-corrected post hoc

tests). In addition, the 3 ratio was significantly more accurate in the metric simple than the nonmetric condition: metric simple versus nonmetric $t(1,19) = 2.88$, $p = .029$ (Bonferronicorrected post hoc tests). No other significant differences in ratio accuracy were found. Examination of histograms and rasters of the reproduced ratios for each participant in each condition showed no evidence that participants were ‘‘regularizing’’ the nonmetric rhythms, that is, reproducing them using integer ratios instead of noninteger ratios. Overall, in the metric simple condition, participants did not truncate the longer ratios as much as they did in the other conditions. Thus, the metric simple condition had not only the greatest number of correctly reproduced sequences, but also more accurate timing of the longest intervals within those sequences. Discrimination Results Based on extensive pilot testing, a discrimination task that equalized behavioral performance was created (see Methods), thus removing confounds of difficulty between conditions. In fMRI, difficulty confounds might have led to activation differences between rhythm conditions that were unrelated to beat processing. Behavioral performance across groups and conditions was similar. Mean d0 and percent correct scores for each condition were as follows: metric simple, d0 = 2.5, percent correct = 87%; metric complex, d0 = 2.2, percent correct = 84%; nonmetric, d0 = 2.4, percent correct = 84%. For each group, musicians: d0 = 2.6, percent correct = 87%; nonmusicians: d0 = 2.2, percent correct = 82%. There were no main effects or interactions between conditions or groups on percent correct or d0 scores, as shown by a 3 2 repeated measures ANOVA with Rhythm type as the within-subjects factor and Musical training (musician, nonmusician) as the between-subjects factor: Rhythm type: d0 : $F(2,50) = 1.44$, $p = .25$, percent correct: $F(2,50) = 1.86$, $p = .17$; Figure 2. Reproduction results. Graph demonstrating the percentage of sequences performed correctly for each of the rhythm conditions. **$p < .001$. 898 Journal of Cognitive Neuroscience Volume 19, Number 5 Musical training: d0 : $F(1,25) = 2.41$, $p = .13$, percent correct: $F(1,25) = 1.85$, $p = .19$. Figure 3 shows the percent correct scores for musicians and nonmusicians across the different rhythm conditions. Reaction times were not analyzed because participants were not asked to make a speeded response. Although behavioral performance was equal across conditions, the data indicate this is not due to floor or ceiling effects. Functional Imaging Results All analyses presented here were conducted on the first two presentations of the rhythms to exclude activation due to deviant detection, decision making, and response preparation during the third rhythm presentation, and motor activation during the subsequent response. The activity therefore likely reflects listening to and maintaining in memory two identical presentations of a rhythm. Figure 4 shows the results of the random effects analysis of all rhythms–rest, collapsed across group and condition. Activation was observed in the pre-SMA/SMA, PMd, basal ganglia, cerebellum, superior temporal gyrus (STG), and ventrolateral prefrontal cortex/insula, all bilaterally (see Table 2 for Z scores of local maxima). For these experiments, we created one set of sequences (the metric simple condition) that were predicted to induce a beat through the presence of regular perceptual accents (Essens, 1995; Essens & Povel, 1985; Povel & Essens, 1985). These sequences were reproduced more accurately than sequences composed of identical intervals, but ordered in such a way as to not induce a beat. Because the sequences were so closely matched, we provisionally concluded that the differences in performance were due to the predicted differences in beat induction. As the behavioral data showed Figure 4. Brain activation during all rhythm conditions–rest. The cortical and cerebellar activations from this contrast defined functional ROIs for further analysis. Z score of 3.3 = $p < .01$, whole-brain corrected (FDR). PMd = dorsal premotor area; SMA = supplementary motor area; STG = superior temporal gyrus; VI = cerebellar crus VI. x, y, and z refer to axes in stereotaxic space. Table 2. Stereotaxic Locations of Peak Voxels in All Rhythms–Rest Contrast Brain Region Z Score p x y z L pre-SMA/SMA 5.03 <.001 9 6 60 R pre-SMA/SMA 4.97 <.001 3 6 66 L putamen 5.67 <.001 24 6 9 R putamen 5.08 <.001 21 6 6 L premotor 5.3 <.001 54 0 51 R premotor 5.24 <.001 54 0 45 R cerebellum 4.68 <.001 30 66 27 L

cerebellum 4.41 <.001 30 66 24 R superior temporal gyrus 6.02 <.001 60 33 6 L superior temporal gyrus 5.8 <.001 57 15 9 L superior temporal pole 4.68 <.001 57 6 3 R inferior frontal 4.52 <.001 27 30 15 This table shows the brain region, p and Z values, and stereotaxic coordinates (in millimeters) of peak voxels in MNI space. Thresholded at $p < .001$, whole-brain corrected (FDR). R = right; L = left; SMA = supplementary motor area. Figure 3. Behavioral data collected during fMRI experiment. The graph demonstrates the percentage of trials discriminated correctly by musicians (mus) and nonmusicians (non) for each of the rhythm conditions. There are no significant differences between groups or conditions. Figure 5. Brain regions more active for metric simple than metric complex or nonmetric rhythms. Z score of 3.43 = $p < .05$, whole-brain corrected (FDR). Grahn and Brett 899 that the metric simple condition was performed significantly better than the other two conditions, we compared activation in the metric simple condition to that in the metric complex and nonmetric conditions. We suggest that this comparison is between beat-inducing and non-beat-inducing rhythms. Increased activation for metric simple rhythms was observed bilaterally in the putamen and superior temporal gyri, as well as left inferior frontal gyrus, shown in Figure 5. See Table 3 for Z scores of local maxima. The ROI analysis (shown in Figure 6) found that the metric simple condition compared to the metric complex condition significantly activated the pallidum, putamen, caudate, pre-SMA/SMA, and STG bilaterally. The same pattern was observed when the metric simple condition was compared to the nonmetric condition, although the caudate no longer reached significance (t values for both contrasts shown in Table 4). No significant differences in activation were seen between the metric complex and nonmetric rhythms. In addition, Table 3. Stereotaxic Locations of Peak Voxels in Metric Simple–Metric Complex and Nonmetric Contrast Brain Region Z Score p x y z L superior temporal gyrus 4.60 .039 51 3 3 3.87 .040 51 9 3 R superior temporal gyrus/ insula 3.78 .045 42 36 18 R insula 3.92 .040 45 6 6 3.87 .040 30 21 12 L putamen 4.47 .039 27 0 9 4.19 .039 27 0 0 3.77 .045 27 12 6 R putamen 4.31 .039 24 0 9 4.31 .039 24 12 6 4.24 .039 24 3 9 L inferior frontal gyrus 4.03 .040 51 33 6 L superior frontal gyrus 4.01 .040 12 69 18 R amygdala 3.88 .040 21 9 15 This table shows the brain region, p and Z values, and stereotaxic coordinates (in mm) of peak voxels in MNI space. Thresholded at $p < .05$, whole-brain corrected (FDR). R = Right, L = Left. Figure 6. Graph of activation during each rhythm condition– rest in each ROI. Metric complex and nonmetric activations in all areas were not significantly different from each other. *$p < .05$ for both metric simple versus metric complex and metric simple versus nonmetric (except in the caudate, where only the metric simple versus metric complex difference reaches significance). R = right; L = left; SMA = supplementary motor area. Table 4. t Values for Metric Simple–Metric Complex, and Metric Simple–Nonmetric Contrasts, for Each ROI t Value ROI Metric Simple–Metric Complex Metric Simple– Nonmetric L superior temporal gyrus 4.13*** 2.08* R superior temporal gyrus 3.91*** 1.72* Pre-SMA/SMA 2.36* 2.12* L caudate 1.83* 1.1 (ns) R caudate 2.06* 1.19* L pallidum 2.66** 1.74** R pallidum 3.45*** 2.78*** L putamen 4.05*** 3.4*** R putamen 3.65*** 2.97*** R premotor cortex 1.25 (ns) 0.46 (ns) L premotor cortex 1.49 (ns) 0.58 (ns) R cerebellum 0.48 (ns) 0.22 (ns) L cerebellum 0.71 (ns) 0.22 (ns) ns = not significant; R = right; L = left; SMA = supplementary motor area. *$p < .05$. **$p < .01$. ***$p < .001$. 900 Journal of Cognitive Neuroscience Volume 19, Number 5 none of the areas were activated significantly more by the metric complex or nonmetric rhythms than the metric simple rhythms. This finding confirms that removal of difficulty confounds was successful: If the metric complex and nonmetric conditions were more difficult or required greater attentional or working memory demands, increased, not decreased, activity would be expected in the dorsolateral prefrontal and anterior cingulate cortices (Duncan & Owen, 2000). To verify this had not occurred, a whole-brain, random effects analysis was conducted, contrasting metric complex and nonmetric rhythms to metric simple rhythms (i.e., all non-beat-inducing–beat-inducing rhythms). Even at a much reduced statistical threshold

all non-beat inducing–beat inducing rhythms). Even at a much reduced statistical threshold ($p < .5$, FDR corrected), no significant activation was observed. The ROI analysis found that musicians showed several areas of greater activation compared to nonmusicians (see Figure 7). Musicians activated the pre-SMA/SMA, bilateral cerebellum, and right PMd significantly more than did nonmusicians in all rhythm conditions compared to rest (see Table 5 for t values). Further analysis showed no significant interactions between group and rhythm type. In addition, a correlation analysis was performed to determine if a relationship between activation in any of the ROIs correlated with behavioral discrimination performance. No significant results were found, probably due to the low variability in behavioral performance.

DISCUSSION

Previous work indicates that rhythms encoded in relationship to a beat are reproduced more accurately than rhythms that are not (Patel et al., 2005; Essens & Povel, 1985). In this experiment, we compared the performance of metric simple rhythms (which had regular perceptual accents) to that of metric complex rhythms (which did not). If regular perceptual accents induce a beat (as predicted by the Povel and Essens model [Essens, 1995; Essens & Povel, 1985]), then metric simple rhythms should be more accurately reproduced. This is indeed what we found. Significantly more metric simple rhythms were reproduced accurately. In addition, shortening of the longest intervals was observed during reproduction in all rhythm types, but this shortening was significantly less in the metric simple condition. Given that the metric simple and metric complex conditions were identical apart from whether the arrangement of the intervals produced regular or irregular perceptual accents, we feel that the most plausible explanation for these effects is that, as predicted, a regular beat was induced in the metric simple condition. The reproduction results suggest that integer ratios and regular perceptual accents are required for beat induction. However, as we did not succeed in creating a condition with regular perceptual accents and noninteger ratios, it is possible that regular perceptual accents alone could induce a beat. This remains an interesting avenue for future research. In contrast to previous research (Sakai et al., 1999), we find that integer ratios alone appear to be insufficient for beat induction, as the number of correctly reproduced metric complex (integer ratios) and nonmetric (noninteger ratios) rhythms was not significantly different in this experiment. The difference between previous work and the current experiments likely arises because the previous study did not assess accent structure. Therefore, the integer ratios

Figure 7. Activation during all rhythms–rest for musicians and nonmusicians. Graph of activation collapsed across conditions, for pre-SMA/SMA, right and left cerebellum, and right premotor area. *$p < .05$. mus = musician; non = nonmusicians.

Table 5. t Values for Activation Differences between Musicians and Nonmusicians in Selected ROIs

ROI	t Value
Pre-SMA/SMA	1.99*
R premotor cortex	2.99**
L premotor cortex	0.75 (ns)
R cerebellum	2.77**
L cerebellum	2.91**
L superior temporal gyrus	0.30 (ns)
R superior temporal gyrus	1.1 (ns)
L caudate	0.32 (ns)
R caudate	0.98 (ns)
L pallidum	1.26 (ns)
R pallidum	0.47 (ns)
L putamen	0.76 (ns)
R putamen	0.21 (ns)

ns = $p > .05$. R = right; L = left; SMA = supplementary motor area. *$p < .05$. **$p < .01$.

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condition in that study contained sequences with varying levels of regularity in the accent structure; the sequences with greater accent regularity may be responsible for the better performance. In the current study, accent structure was manipulated to be regular or irregular, allowing us to assess the role of accents separately from that of integer ratios. When accent structure is accounted for, then the presence of integer ratios is not enough to improve behavioral rhythm performance. Another interesting phenomenon reported in temporal reproduction studies is that some participants ''regularize'' noninteger ratio sequences during performance, such that the noninteger ratios are distorted into integer ratios. We find no evidence of regularization in our study, although this is likely due to the stimuli we used. In most previous studies that find regularization (Collier & Wright, 1995; Essens, 1986; Essens & Povel, 1985) only one ratio (e.g., 1:2.5 or 1:3.3) is present in any given sequence or block of stimuli. Therefore, the perception of the unit level (1) and the level that is the noninteger multiple of that unit (2.5 or 3.3), and the resulting relationship between the levels is quite

multiple of that unit (2.5 or 3.5), and the resulting relationship between the levels is quite easy to discern. The perception of this relationship may then allow participants to stretch or shrink the noninteger ratio in order to make it into an integer multiple of the unit level. This regularization presumably decreases the timing difficulty of the task. Other work (Sakai et al., 1999) has used more than one noninteger ratio (1:2.5:3.5), but in this case, only three (of 6) participants showed regularization, and only for some sequences. Another contributing factor to whether regularization occurs may be the use of block presentations of the noninteger ratio sequences (Sakai et al., 1999) or high numbers of sequence repetitions (Collier & Wright, 1995; Essens, 1986; Essens & Povel, 1985), giving participants a greater number of exposures to perceive the relationships between the intervals. Again, this perception of the relationship may lead subjects to regularize in order to simplify the task. When many ratios are present, such as 1:1.4:3.5:4.5 in the current study, it is presumably less clear what the relationships between the unit level (1) and the other levels (1.4, 3.5, and 4.5) are. The relationships are further clouded by the presence of other ratios between intervals in the sequence (1.4:3.5, 1.4:4.5, and 3.5:4.5). These sequences may be too complex for participants to determine how to go about regularizing them, especially in the current study, where there are only a small number of presentations of each rhythm and no blocked presentation of the rhythm types. Finally, other work has used noninteger ratios rhythms and does not report regularization, although perhaps this specific issue was not assessed in detail (Lewis et al., 2004; Ulle´n, Forssberg, & Ehrsson, 2003). It should be noted that our account for lack of regularization, is speculative and requires evidence from further investigations in which the number of noninteger ratios present in a sequence, or the number of sequence presentations, is systematically manipulated and the effects on reproduction performance are assessed.
Moving on to the fMRI data collected in the second experiment, we find that a bilateral network of motor areas is activated when rhythms are perceived, even when no movement is made. When listening to all the rhythms compared to rest, bilateral activation was observed in the pre-SMA/SMA, PMd, basal ganglia, cerebellum, superior temporal gyri, and ventrolateral prefrontal cortex/anterior insula. The lack of activation in primary motor cortex suggests that participants complied with instructions not to move any part of their body during presentation of the rhythms, and thus the activation observed is likely due only to perception of rhythm. These findings are consistent with other studies (Lewis et al., 2004; Schubotz, Friederici, & von Cramon, 2000; Penhune et al., 1998) confirming that a bilateral network of motor areas mediate perception of rhythm in addition to rhythm production. These data may also suggest that rhythm perception may lie more within the ‘‘automatic’’ timing system proposed by Lewis and Miall (2003), as this system is composed mainly of motor areas and is most involved in timing of subsecond intervals. However, the automatic system is thought to operate mainly for predictable or overlearned stimuli, and without ‘‘attentional modulation.’’ The stimuli here were not learned and in many cases were unpredictable. It also seems unlikely that perception of such complicated rhythms would occur without attention, therefore it may be that the automatic system is responsible for perception of the individual intervals that compose the sequences, but does not mediate cohesive perception of the rhythm as a whole. The fMRI data provide additional confirmation of the importance of regular perceptual accents in rhythm perception. Listening to metric simple rhythms significantly increased activity bilaterally in the basal ganglia, anterior superior temporal gyri, left inferior frontal gyrus, and the pre-SMA/SMA (although the latter activation only reached significance in the ROI analysis), compared to the metric complex and nonmetric conditions. A role for the basal ganglia and SMAs in beat induction is consistent with their involvement in motor prediction (the spontaneous response to hearing a beat is often to move at the time when the next beat is predicted). The anatomy supports their mutual contribution, as the basal ganglia and pre-SMA/SMA are richly connected through striato–thalamo–cortical loops (Inase & Tanji, 1994; Alexander, DeLong, & Crutcher, 1992)

and are involved in timing (Macar, Anton, Bonnet, & Vidal, 2004; Ferrandez et al., 2003), including timing of future movements (Sardo, Ravel, Legallet, & Apicella, 2000; Rao et al., 1997). Patients with lesions in SMAs are impaired at reproducing temporal sequences from memory (Halsband et al., 1993). However, further research is needed to clarify whether increased activity in basal ganglia and pre-SMA/SMA underlies the spon902 Journal of Cognitive Neuroscience Volume 19, Number 5 taneous movement that often spontaneously occurs to the beat. The bilateral anterior superior temporal gyri were also more active during metric simple rhythms compared with metric complex and nonmetric rhythms. The peak of this activation is 3 cm anterior to the peak of the auditory cortex activation observed in the all rhythms minus rest contrast, placing it in the anterior secondary auditory cortex. Activity here has been observed for auditory imagery (Zatorre, Halpern, Perry, Meyer, & Evans, 1996). Accordingly, our participants may have been able to form a better auditory image of the beatbased rhythms, consistent with the better performance of these rhythms in the reproduction experiment. Alternatively, the anterior auditory areas may be important for perceiving the beat in the first place. This is consistent with neuropsychological work (Liegeois-Chauvel, Peretz, Babai, Laguitton, & Chauvel, 1998) that shows that the anterior STG is necessary for normal musical meter perception (determining if beat groupings are in a ''waltz'' or ''march'' meter). Beat perception itself was not directly tested in the patients, but musical meter perception depends fundamentally on perceiving the underlying beat (London, 2001). Intriguingly, resection in either hemisphere produced impairment, consistent with the bilateral nature of the activation in the current study. A visual rhythm condition in future experiments may help determine whether the auditory cortex makes a supramodal contribution to rhythm processing, or if its role is restricted to the auditory modality. Difficulty can be a major confound in fMRI experiments. Increased difficulty in a wide range of paradigms cause greater activation in the dorsolateral prefrontal and anterior cingulate cortices, suggesting a specific network for effortful processing across domains (Duncan & Owen, 2000). To avoid difficulty confounds in the fMRI experiment, we used a task that had similar levels of performance across conditions. Reassuringly, although the metric complex and nonmetric conditions were the most difficult in the reproduction task, they produced less, not more activity in the fMRI study. In addition, the timing requirements of the individual intervals across the conditions were very well matched. Taken together, these findings indicate that it is unlikely that the increased activation in the metric simple condition can be explained by difficulty. Nevertheless, it was initially surprising that no brain areas were significantly more active in the metric complex or nonmetric conditions than in the metric simple condition, given that the reproduction study indicates the metric complex and nonmetric conditions are more difficult. Working memory studies, however, indicate that prefrontal areas can show increased activity when encoding easier stimuli compared with harder stimuli if the easier stimuli contain structure (Bor, Cumming, Scott, & Owen, 2004; Bor, Duncan, Wiseman, & Owen, 2003). The prefrontal area activated in those studies is very near the left inferior frontal gyrus activation found in this study. This suggests that the beat in the metric simple condition may be providing a regular structure (sometimes called a ''temporal grid''; Povel, 1984) that aids working memory performance for the rhythms. We also found that activation to the metric complex and nonmetric conditions did not significantly differ. Thus, the fMRI results are in contrast to a previous study (Sakai et al., 1999), which reported different patterns of activation for sequences with integer- and noninteger ratio intervals (although the two conditions were not statistically compared, so it is unclear if the differences are reliable). However, as mentioned before, the integer ratio sequences in that study likely contained varying levels of regularity in the accent structure, as the authors did not consider perceptual accents in their stimuli; thus, any differences may not be due to the presence of integer ratios versus noninteger ratios per se. These data may illuminate a controversy about the existence of a ''beat-based'' (or entrainment) timer

(Pashler, 2001). A beat-based timer is hypothesized to encode intervals in reference to an underlying isochronous beat (using a beat to measure if an interval is one beat long, two beats long, etc.). Several studies have examined whether a beat-based timer exists, and if so, whether it can improve timing. Generally, these studies test how accurately humans time a single time interval, under conditions that are or are not conducive to using beat-based timing. The results are conflicting (McAuley & Jones, 2003; McAuley & Kidd, 1998; Vos, van Assen, & Franek, 1997; Schulze, 1978; cf. Pashler, 2001; Ivry & Hazeltine, 1995; Keele, Nicoletti, Ivry, & Pokorny, 1989) perhaps because timing of a single interval is most frequently tested. The reproduction data here, acquired on a more complicated temporal rhythm task, show a substantial performance benefit for rhythms that are designed to induce a beat. These data suggest that a beat-based mechanism does exist, and improves timing performance when more difficult temporal tasks are tested. In addition, a specific network of areas was more active during perception of beat-inducing rhythms compared with other rhythms, even when no significant behavioral performance differences were observed. This suggests that the beat-based system can be active even when no behavioral performance benefit is observed. Thus, the fact that some previous work does not find a behavioral beat-based timing benefit does not necessarily mean that such a mechanism was not active or used. Interestingly, the observed cerebellum and premotor cortex activations were not significantly different across the three rhythm types. Many other studies show involvement of these areas in temporal processing (Penhune & Doyon, 2002; Ramnani & Passingham, 2001), but they appear not to have a specific role in beat-based timing. Musically trained participants recruit these areas more than untrained participants do, although behavioral discrimination performance is the same between these Grahn and Brett 903 groups. Premotor areas have been implicated in rehearsal during working memory tasks (Smith & Jonides, 1999) and general working memory operations that are not task or material specific (Cabeza & Nyberg, 2000); accordingly, musicians may have used rehearsal strategies to a greater degree than did nonmusicians. Alternatively, the cerebellum and/or premotor areas may be responsible for more basic timing processes that are required to encode the time intervals in the first place. The basal ganglia and pre-SMA/SMA (perhaps also with the anterior STG) may then be responsible for detecting or relating that information to an isochronous beat interval. If this relationship can be established, a more stable and accurate representation of the sequence can occur, which would result in improved reproduction performance. The fact that musicians do not activate these areas more than the nonmusicians do supports the theory that forming a temporal representation in relation to a beat is a universal process; nearly all humans can perceive a beat in music, without special training or practice, but merely through exposure to beat-based patterns (Drake, 1998). One theory on the roles of the basal ganglia and cerebellum suggests that the latter subserves timing in the milliseconds to seconds range, and the former subserves timing in the seconds to minutes range (Ivry, 1996). Although our experiment did not directly test this theory, the results suggest that both areas are involved in timing in the milliseconds to seconds range, but the basal ganglia are more involved when the structure of a rhythm allows beat-based timing to be used. This suggests that the types of deficits found on timing tasks when testing neuropsychological patients will be dependent on the type of timing that can be used to accomplish the task. As the majority of neuropsychological studies test timing of isochronous intervals, which do not reliably show beat-based timing advantages, future studies using complex sequences will be important to clarify the roles of the basal ganglia and cerebellum in timing. For example, the current results suggest that patients with basal ganglia dysfunction would be impaired at using beatbased timing. If so, deficits may be reliably observed only for performance of more complicated rhythmic stimuli, not performance of isochronous intervals. In conclusion, regular accent structure appears to be critical for hearing a beat in rhythm. When regular perceptual accents are present, reproduction performance is improved. Although several brain

areas are activated during rhythm perception, the basal ganglia, pre-SMA/ SMA, and anterior superior temporal gyri show increased activity specifically to beat-based rhythms, in both musicians and nonmusicians. Reprint requests should be sent to Jessica A. Grahn, MRC Cognition and Brain Sciences Unit, 15 Chaucer Road, Cambridge CB2 2EF, UK, or via e-mail: Jessica.grahn@mrc-cbu. cam.ac.uk. REFERENCES Alexander, G. E., DeLong, M. R., & Crutcher, M. D. (1992). Do cortical and basal ganglionic motor areas use ''motor programs'' to control movement? Behavioral and Brain Sciences, 15, 656–665. Artieda, J., Pastor, M. A., Lacruz, F., & Obeso, J. A. (1992). Temporal discrimination is abnormal in Parkinson's disease. Brain, 115, 199–210. Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. Journal of the Royal Statistical Society, Series B, 57, 289–300. Bor, D., Cumming, N., Scott, C. E. L., & Owen, A. M. (2004). Prefrontal cortical involvement in verbal encoding strategies. European Journal of Neuroscience, 19, 3365–3370. Bor, D., Duncan, J., Wiseman, R. J., & Owen, A. M. (2003). Encoding strategies dissociate prefrontal activity from working memory demand. Neuron, 37, 361–367. Brochard, R., Abecasis, D., Potter, D., Ragot, R., & Drake, C. (2003). The ''ticktock'' of our internal clock: Direct brain evidence of subjective accents in isochronous sequences. Psychological Science, 14, 362–366. Brotchie, P., Iansek, R., & Horne, M. K. (1991). Motor function of the monkey globus pallidus. 2. Cognitive aspects of movement and phasic neuronal activity. Brain, 114, 1685–1702. Cabeza, R. C., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. Journal of Cognitive Neuroscience, 12, 1–47. Collier, G. L., & Wright, C. E. (1995). Temporal rescaling of simple and complex ratios in rhythmic tapping. Journal of Experimental Psychology: Human Perception and Performance, 21, 602–627. Coull, J. T., Vidal, F., Nazarian, B., & Macar, F. (2004). Functional anatomy of the attentional modulation of time estimation. Science, 303, 1506–1508. Cunnington, R., Windischberger, C., Deecke, L., & Moser, E. (2002). The preparation and execution of self-initiated and externally-triggered movement: A study of event-related fMRI. Neuroimage, 15, 373–385. Cusack, R., & Papadakis, N. (2002). New robust 3-D phase unwrapping algorithms: Application to magnetic field mapping and undistorting echoplanar images. Neuroimage, 16, 754–764. Dhamala, M., Pagnoni, G., Wiesenfeld, K., Zink, C. F., Martin, M., & Berns, G. S. (2003). Neural correlates of the complexity of rhythmic finger tapping. Neuroimage, 20, 918–926. Drake, C. (1998). Psychological processes involved in the temporal organization of complex auditory sequences: Universal and acquired processes. Music Perception, 16, 11–26. Drake, C., Jones, M. R., & Baruch, C. (2000). The development of rhythmic attending in auditory sequences: Attunement, referent period, focal attending. Cognition, 77, 251–288. Drake, C., Penel, A., & Bigand, E. (2000). Tapping in time with mechanically and expressively performed music. Music Perception, 18, 1–24. Duncan, J., & Owen, A. M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends in Neurosciences, 23, 475–483. Essens, P. J. (1986). Hierarchical organization of temporal patterns. Perception & Psychophysics, 40, 69–73. Essens, P. J. (1995). Structuring temporal sequences: Comparison of models and factors of complexity. Perception & Psychophysics, 57, 519–532. Essens, P. J., & Povel, D. J. (1985). Metrical and nonmetrical 904 Journal of Cognitive Neuroscience Volume 19, Number 5 representations of temporal patterns. Perception & Psychophysics, 37, 1–7. Ferrandez, A. M., Hugueville, L., Lehe´ricy, S., Poline, J. B., Marsault, C., & Pouthas, V. (2003). Basal ganglia and supplementary motor area subtend duration perception: An fMRI study. Neuroimage, 19, 1532–1544. Freeman, J. S., Cody, F. W., & Schady, W. (1993). The influence of external timing cues upon the rhythm of voluntary movements in Parkinson's disease. Journal of Neurology, Neurosurgery, and Psychiatry, 56, 1078–1084. Genovese, C. R., Lazar, N. A., & Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage, 15, 870–878. Grahn, J. A., & Brett, M. (2005). Rhythm processing in patients

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 Special issue: Research report The primal role of the vestibular system in determining musical rhythm

Laurel J. Trainora,b, *, Xiaoqing Gaoa , Jing-jiang Leia , Karen Lehtovaaraa and Laurence R. Harrisc aDepartment of Psychology, Neuroscience & Behaviour and the McMaster Institute for Music and the Mind, McMaster University, Hamilton, Ontario, Canada b Rotman Research Institute, Baycrest Hospital, Toronto, Ontario, Canada cCentre for Vision Research, York University, Toronto, Ontario, Canada article info Article history: Received 19 January 2007 Reviewed 30 May 2007 Revised 20 June 2007 Accepted 4 October 2007 Published online 7 November 2008 Keywords: Vestibular stimulus Galvanic stimulation Musical rhythm Vestibulo-auditory interaction abstract Previous studies have indicated that physical movement on either every second or on every third beat of an unaccented auditory rhythm pattern can disambiguate whether it is perceived in duple time as a march or in triple time as a waltz. Here we demonstrate that this disambiguation can also be accomplished by direct galvanic stimulation of the vestibular system. The galvanically induced sensation, without any actual movement, that the head moved from side to side on either every second or on every third beat of the ambiguous auditory rhythm pattern strongly biased whether adults perceived it as being in duple or in triple time. These results imply that the vestibular system plays a primal role in the perception of musical rhythm.

1. Introduction

Physical movement and the perception of musical rhythm seem to be closely bound. Historically, music and dance have evolved together, and across all cultures, people move in synchrony to musical rhythms (Arom, 1991; Clarke, 1999; Cross, 2003; Molinari et al., 2003; Todd, 1995; Wallin et al., 2000). Body movement is commonly used in music education in order to teach rhythmic patterns, further suggesting a link between movement and the perception of rhythm. For example, in Kindermusik classes infants are passively moved to music with different rhythmic patterns (Cutietta, 2001) and more advanced students in Dalcroze Eurhythmics classes learn to internalize rhythmic patterns through physical movement in time and space (Jaques-Dalcroze, 1920; Juntunen and Hyvo¨nen, 2004). Adults and children can readily tap to the strong beats of a rhythmic pattern, regardless of musical training (Drake et al., 2000) and tapping behaviour reflects their auditory representations of the rhythm pattern (Repp, 2005, review). Clearly there is a deep connection between movement and rhythm but how might this have come about?

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Perhaps the most common form of movement with a tempo is walking. That locomotion involves regularly spaced movements of the arms, legs, and the head has been observed for a long time. Curiously, however, the tempo range of locomotion movements turns out to correspond closely to the range over which a beat can be felt – pulse separations of between about 300 and 900 msec (e.g., Fraisse, 1982; Clarke, 1999). At tempos slower than this, auditory events are not connected into a perceptual pattern and at faster tempos, events cannot be sufficiently individuated. Furthermore an individual's preferred auditory beat rate correlates with anthropometric variables such as height, leg length, shoulder breadth, and body weight (Todd et al., 2007) that are in turn related to an individual's locomotion tempo. These correlations provide circumstantial evidence for a link between the cues generated by locomotion and the auditory perception of tempo. But musical rhythm can be much more complex than the simple repetitive frequency of walking. One of the remarkable abilities of humans is that we can entrain and feel musical beats at several different tempos. Although many non-human

animals engage in rhythmic behaviours (e.g., apes will drum and certain birds will peck rhythmically), only a few species entrain their movements to different externally defined tempos (e.g., cockatoos, Patel et al., 2008). Indeed, it appears that only species that engage in vocal learning exhibit rhythmic entraining (Schachner et al., 2008). Being able to produce different tempos synchronized with other players is a likely prerequisite for human musical behaviour (Trainor, 2007). Humans can extract a complex metrical hierarchy from a rhythm pattern beyond that directly present in the stimulus (e.g., Lerdahl and Jackendoff, 1983). For example, the tactus level (tempo at which you would tap your foot) of a rhythm pattern is readily extracted, even from patterns that may not always contain sound events on the beats that are perceived as strong (i.e., accented). A tactus level can also be derived when the tempo is not steady or even if the rhythm contains accented ''off-beat'' sound events, as in the syncopations of jazz. Furthermore, the perceived metrical structure is hierarchical. For example, the beats of the tactus can be subdivided into groups of two sub-beats (as in a march) or three sub-beats (as in a waltz), producing a fast tempo that can be perceived at the same time as the ongoing slower tactus. Tempos can also be slowed down by grouping. For example, every second or every third tactus-level beat may be more strongly accented, producing a slower rhythm. Metrical structure is normally derived from the pattern of physically accented beats – e.g., sound events that are longer, louder, and/or higher in pitch. However, physical movement can also influence the metrical interpretation of an ambiguous rhythm pattern (Phillips-Silver and Trainor, 2005, 2007). Just as ambiguous visual stimuli can be created that can be perceived in two distinct ways, such as the famous Ruben drawing of a vase, the edges of which can alternatively be perceived as two inward-looking faces, Phillips-Silver and Trainor created an ambiguous auditory stimulus. It consisted of a repeating six-beat drum pattern with no accented notes (see Fig. 1). If every second beat was ''heard'' as strong, the rhythm took on a march-like quality (duple meter) whereas if every third beat was ''heard'' as strong, the rhythm took on a waltz-like quality (triple meter). The two interpretations of the pattern sounded completely different, just as the two interpretations of the Ruben figure look completely different. And just as only one interpretation of an ambiguous visual pattern can be perceived at any one time (either a vase or two faces), only one interpretation of the ambiguous auditory rhythm could be perceived at any one time. A physical bouncing movement on either every second beat or on every third beat of the ambiguous auditory rhythm pattern biased which interpretation was perceived in both infant (Phillips-Silver and Trainor, 2005) and adult subjects (Phillips-Silver and Trainor, 2007). Visual information was not necessary for the effect as the results were similar when the subjects were blindfolded. On the other hand, physical movement of the subject was critical as passively observing the experimenter moving did not bias whether the ambiguous rhythm sounded like a march or a waltz in either infants or adults. These studies demonstrated the primal role of movement in determining musical rhythm but could not indicate which aspect(s) of movement were critical in determining the perceived metrical interpretation. What correlate of movement might establish the correlation between physical movement and auditory rhythm? Candidates include motor planning (efferent copy of motor signals), sensory feedback arising from the consequences of the movement such as tactile or visual information, or sensory feedback directly about the movement itself arising from proprioceptive sources. A major source of proprioceptive information concerning whole body movement comes from the vestibular system. Passive movement of the legs on either every second or third beat of an ambiguous auditory rhythm did not bias whether adults perceived a duple or triple metrical structure, but passive movement of the head on these beats did (Phillips-Silver and Trainor, 2008). Given that both the legs and the head are strongly involved in locomotion, sensorimotor planning, tactile input, and proprioceptive input, but only movement of the head generates a vestibular Fig. 1 – The auditory rhythm. Thin vertical

lines represent unaccented snare drum beats. Thick vertical lines represent accented snare drum beats. Oblique lines represent rests. The top line represents the ambiguous rhythm used during familiarization. The other two lines represent the rhythms used during the test phase. The middle line represents the rhythm with auditory accents in duple (march) time and the bottom line the rhythm with auditory accents in triple (waltz) time. 36 cortex 45 (2009) 35–43 Author's personal copy signal, these results suggest that vestibular input may be crucial to the multisensory interaction between movement and auditory rhythm. The hypothesis of vestibular involvement is consistent with the early emergence of movement/ auditory interactions in infancy and the early maturation of the vestibular system, as illustrated by the delight with which premobile infants greet bouncing, rocking, and swooping stimulation. In this paper, we dissociate the vestibular signal from aspects of movement by stimulating the vestibular system directly in the absence of physical movement using galvanic stimulation (see Buys, 1909; Goldberg et al., 1984; Mars et al., 2005; Wardman et al., 2003; Zink et al., 1997). Subjects listened to an ambiguous rhythm pattern while we stimulated the vestibular nerve in such a way as to create the sensation of a side-to-side movement of the head, timed to occur on every second beat of the auditory rhythm for half of the subjects and on every third beat for the other half. We provide evidence that a vestibular signal alone is sufficient to bias the metrical interpretation of an auditory rhythm pattern. 2. Method 2.1. Participants Participants were 23 (6 male, 17 female) university undergraduate students (aged 18–25 years, mean age ¼ 19 years) enrolled in an introductory psychology course who received course credit for participation. All of the participants had no known hearing deficits and were unaware of the purpose of the study. Half of the participants were randomly assigned to the experimental condition and half to the control condition. Two additional subjects were excluded, one due to equipment failure and one for producing data more than 3 standard deviations from the mean. The experimental group was comprised of 11 subjects; the control group was comprised of 12 subjects. Subjects had between 0 to 14 years of music lessons (mean ¼ 4.3 years for the experimental group and 4.1 years for the control group). Procedures were approved by the McMaster University Ethics Board and subjects gave written consent to participate. 2.2. Stimuli 2.2.1. Auditory stimuli Both the familiarization and test stimuli were similar to those of Phillips-Silver and Trainor (2005) and were presented in a sound-attenuating chamber over a noise floor of 25 dB(A). The vestibular stimulation was presented with pulses every 25.1 msec, so the tempos of the auditory rhythms were chosen to be multiples of this number. The training stimulus consisted of a snare drum timbre downbeat background presented every 1959 msec at 60 dB(A), a slapstick timbre microbeat background presented every 326.5 msec at 50 dB(A) such that 6 microbeats occurred within each period defined by the downbeats, and an ambiguous familiarization rhythm pattern of interest at 60 dB(A) that was superimposed on the background beats. The rhythm pattern of interest consisted of four snare drum sounds with stimulus onset asynchronies (SOAs) of 653–326.5– 326.5–653 msec (where the first sound coincided with the background downbeat) resulting in a rhythm of sound-restsound-sound-sound-rest (see Fig. 1). Note that this rhythm pattern is ambiguous because it can be perceived either as consisting of three groups of two beats, with every second beat accented as in a march (SOUND-rest-SOUND-soundSOUND-rest), or as two groups of three beats, with every third beat accented, as in a waltz (SOUND-rest-sound-SOUNDsound-rest), even though these accents are not physically present. The sounds can be heard at http://psycserv. mcmaster.ca/ ljt/research.htm. The two auditory test stimuli were identical to the training rhythm described above, except that the rhythm pattern of interest was disambiguated by physically accenting some sounds relative to others by playing them louder (60 vs. 55 dB). Specifically, for the duple rhythm, every second beat was physically accented as in a march (SOUND-rest-SOUNDsound-SOUND-rest), and for the triple rhythm, every third beat was physically

accented as in a waltz (SOUND-restsound-SOUND-sound-rest). In all cases, the beat onset-toonsets fell within the optimal range for tempo discrimination (Fraisse, 1982; Baruch and Drake, 1997). 2.2.2. Vestibular stimulus The vestibular stimulation consisted of a small current applied to electrodes on the mastoid process behind the ears (see Section 2.3). The current waveform consisted of Gaussian-shaped pulses with a peak amplitude of 1 mA and a standard deviation of 100 msec. Positive and negative pulses were presented alternately such that they were out of phase in the two ears (Fig. 2). Three tempos were used for the peak-topeak time interval between stimulations, 653 msec (corresponding to the duple auditory stimulus rate), 979.5 msec (corresponding to the triple auditory stimulus rate), and 816 msec (midway between the duple and triple tempos, used to calibrate individual phase shifts between vestibular stimulation and perceived head movement, see Section 2.5, below). During pilot testing, we examined different waveforms for the vestibular current stimulation, including impulse waves, triangular waves, and sine waves, and found that the Gaussian waveform produced the clearest sensation of the head moving from side to side. 2.3. Apparatus The vestibular stimulus was generated by a Good Vibrations Engineering Ltd. Galvanic Vestibular Stimulation system (GVS). For the experimental group, an electrode was attached to the mastoid process under each of the participant's ears. For the control group, an electrode was attached to each of the participant's elbows (Fig. 3). The electrode was a 2-inch round Proflex CC carbon conductor electrode (Canadian Medical Products Ltd, F2020PF). This electrode material and shape was selected during pilot testing as providing the most comfort and the best sensation of head movement. The auditory stimuli were created using Cakewalk with the snare drum (#229) and slapstick (#244) voices on a Roland 64- Voice Synthesizer Module, digitized with Cool Edit 2000 on a personal computer using an AOpen AW-840 4-channel PCI sound card, and presented by a Power Macintosh 7300/180 cortex 45 (2009) 35–43 37 Author's personal copy computer through a Denon PMA-480R amplifier to two audiological GSI speakers located inside a large Industrial Acoustics Co. sound-attenuating booth with a sound floor of 25 dB(A). The sound booth was set up so that the participant sat between the two speakers, and auditory stimuli were always presented from both speakers. The experiment was controlled from the GVS system, with software running on an IBM Thinkpad 760ED laptop. At the same time that a vestibular stimulus was sent to the subject, a trigger was sent to the Power Macintosh through a custombuilt interface consisting of an opto-isolator. Sounds were presented from the Macintosh using a custom software program that ensured accurate timing. 2.4. Pilot test of phase relations between vestibular stimulation and perceived head movement Pilot testing revealed that with vestibular stimulation of alternating positive and negative Gaussian waveforms that were out of phase between the ears, subjects experienced a side-to-side movement of the head, even though the head actually remained stationary. However, the phase relation between the vestibular stimulation and the time at which the head was perceived to be maximally displaced to the right and to the left varied considerably from person to person. It was essential that the time of perceived maximal head displacement corresponded to the onsets of auditory beats in the main experiment, so it was necessary to characterize the extent of these individual differences and to compensate for them on an individual basis. In order to do this, 5 pilot subjects were given vestibular stimulation alone (i.e., no concurrent sound) in an isochronous rhythm sequence, with the peaks of the vestibular stimulation occurring at 653 msec intervals in one condition (corresponding to the duple auditory stimulus rate) and at 979.5 msec intervals (corresponding to the triple auditory stimulus rate) in a second condition. Subjects were asked to tap along with their perceived side-to-side head movement on a response pad (EGI 200) at the precise times at which their head was maximally displaced to the right and to the left. Subjects were monitored to ensure that they did not make any overt head movements. Fig. 4 shows histograms of the onsetto-onset times of

tapping intervals for two individual subjects for the 979.5 tempo. As can be seen, responses centred on the vestibular inter-stimulus separation times, indicating that the head was perceived to move at the same rate as the vestibular stimulation. Fig. 4 also shows the phase offset between vestibular peak stimulation and the timing of the subjects' taps. As can be seen, this phase varied considerably between subjects. Because we did not want to fatigue the vestibular responses of subjects by running them through a long pilot procedure, a short test was developed to determine the Fig. 3 – Vestibular and control conditions. In the vestibular condition, galvanic stimulation was delivered to the vestibular nerve (left panel) and in the control condition it was delivered to the elbows (right panel). Fig. 2 – The galvanic stimulus delivered to the vestibular system. The left panels represent the Gaussian-shaped electrical stimuli at the 653 msec tempo (duple time) and the right panel the 979.5 msec tempo (triple time). For each panel the stimuli are out of phase across the right (top panels) and left (bottom panels) ears. 38 cortex 45 (2009) 35–43 Author's personal copy approximate phase relation for each individual subject as described below. 2.5. Procedure Subjects were first given a pre-test to determine their individual phase relation between vestibular stimulation and their maximal perceived side-to-side head movement. They were then given a questionnaire about their musical background. This was followed by a familiarization phase in which the ambiguous auditory rhythm pattern was presented concurrently with vestibular stimulation on every second (duple familiarization condition) or on every third (triple familiarization condition) beat of the ambiguous auditory rhythm. In this phase, the control subjects experienced stimulation of their elbows instead of their vestibular nerve. Subjects were monitored to ensure that they did not make any overt head movements. Finally, subjects were given an auditory-alone test with the disambiguated duple and triple auditory stimuli (no vestibular stimulation) and asked to chose which sounded most like what they had heard during the familiarization phase. The entire experiment lasted less than 1 h. All subjects heard exactly the same auditory stimuli throughout the experiment. If there were multisensory interactions between the vestibular and auditory systems, subjects who experienced duple vestibular stimulation should perceive the ambiguous auditory pattern as a march, and hence choose the duple auditory stimulus as sounding most like what they heard during familiarization. On the other hand, those experiencing triple vestibular stimulation would be expected to perceive the ambiguous auditory pattern as a waltz, and choose the triple auditory stimulus as sounding most like what they heard during familiarization. Each of these phases is described in detail below. 2.5.1. Individual phase shift measurement The electrodes were applied behind the ears in the experimental group and to the elbows in the control group. Subjects in the experimental group were told that they might feel their head move from side to side while they heard a repeating tone. Subjects in the control group were told that they might feel a tingling in their elbows. Experimental group subjects were to determine whether the tone came before or after the time at which they perceived their head to be maximally displaced to the right and left. Control group subjects were to determine whether the tone came before or after the tingling they felt in their elbows. A 100 msec 60 dB pure tone at 500 Hz was played repeatedly with an SOA of 816 msec (half way between the two possible stimulation rates used during the experiment that followed) and the vestibular/elbow stimulation was applied at the same rate for 30 sec. Initially, the tone was presented 200 msec offset from the peak of the electrical stimulation. Subjects were asked to indicate whether the sound came before or after the point of maximal perceived head displacement/elbow tingling or whether the two stimuli were concurrent. The phase was then adjusted until the sound and perceived head movement/elbow tingling were reported to be concurrent. Five possible phase shift values were used, 150, 170, 200, 230, 260, and 290, covering the range of phase values measured in the pilot study. Phase shifts used ranged between 170 and 260 msec with a mean of 205 msec (SD ¼ 33.3). Fig. 4 – Distribution of tapping responses

synchronized to illusory perceived head movements evoked by galvanic stimulation illustrated by the responses of two representative subjects. Bin widths are 30 msec. Stimuli were delivered using the pattern illustrated in Fig. 2 with a separation of 979.5 msec. The distributions of inter-tap intervals (left panels) were centred close to the vestibular stimulation rate at 978 msec (SD [72) and 983 msec (SD [80) for each subject. Phase relations (delay in msec between the stimulus and tap, right panels) showed variability across subjects, peaking at 200 msec (SD [102) and 245 msec (SD [71) in subjects A and B, respectively. cortex 45 (2009) 35–43 39 Author's personal copy 2.5.2. Familiarization All subjects listened to one minute of the ambiguous auditory familiarization rhythm. Subjects in the experimental condition received concurrent vestibular stimulation while those in the control group received concurrent elbow stimulation. Within each group, half received duple vestibular/elbow stimulation (i.e., with an SOA of 653 msec, individually phase shifted to be perceived as concurrent with every second beat of the auditory pattern) and half received triple vestibular/ elbow stimulation (i.e., with an SOA of 979.5 msec, individually phase shifted to be perceived as concurrent with every third beat of the auditory pattern). All subjects were tested with eyes closed. Although it is possible that the vestibular stimulation caused some nystagmus, such eye movements are unlikely to influence perceived auditory rhythm directly. The brain largely monitors such eye movements via an efference copy of the vestibular driving signal rather than feed forward proprioceptive input from eye muscles (Bridgeman and Stark, 1991). If the vestibular stimulation we used were to have an effect on the interpretation of auditory rhythm patterns, it would be even more remarkable if it were mediated by eye movements than if it were mediated directly through the vestibular system. The control condition with the electrodes on the elbows would also likely cause some small muscular activity. A lack of effect in this condition would suggest that small muscle movements are insufficient to influence auditory pattern perception. 2.5.3. Testing Immediately following the training phase, the participant was given eight two-alternative forced-choice trials, with auditory presentation alone. Each trial contained a duple and a triple test stimulus. Both of the duple and triple test stimuli were identical to the auditory familiarization stimulus, except that physical accents (see Section 2.2) were present on every second beat for the duple test stimulus, and on every third beat for the triple. The two stimuli on each trial were presented in random order for one cycle or 1959 sec each, separated by 1000 msec. On the first trial, the order was counterbalanced, so that half of the participants in each condition heard the duple rhythm first, and half heard the triple rhythm first. Participants were instructed to choose which of the two stimuli was the same as, or most similar to, the rhythm they had heard in the training phase, and their verbal responses were recorded by the experimenter. 3. Results After vestibular entrainment with 653 msec intervals (corresponding to the beats of the duple interpretation), 87.5 percent of judgements of the rhythm of the ambiguous auditory stimulus were for the duple interpretation; after entrainment with 979.5 msec intervals (corresponding to the beats of the triple interpretation), 70.0 percent of judgements were for the triple interpretation. An ANOVA, with the independent variables experimental condition (vestibular, elbow) and electrical familiarization stimulation (duple, triple) and the dependent variable the proportion of responses in which the duple auditory-alone rhythm was chosen as most similar to what was heard during familiarization, revealed only a significant interaction between experimental condition and familiarization stimulation, $F(1, 19) = 11.3$, $p < .003$. As can be seen in Fig. 5, stimulation of the elbows (control condition) at either frequency during familiarization did not affect whether subjects perceived the ambiguous auditory stimulus in duple or triple form in any systematic way, $p > .4$. On the other hand, vestibular stimulation during familiarization had a significant effect on whether subjects perceived the ambiguous auditory stimulus in duple (march) or triple (waltz) form, $t(10) = 6.3$, $p < .0001$. There were no significant correlations between musical training and

performance for either group. 4. Discussion Previous studies have shown that physical movement plays a critical role in entraining and disambiguating a musical rhythm (Phillips-Silver and Trainor, 2005, 2007). The present study shows that this effect is mediated through the vestibular system. Galvanic stimulation of the vestibular system caused, on average, 79% of perceptual judgements to move towards the auditory interpretation entrained by the vestibular stimulation, whereas control stimulation caused no such shift in auditory pattern perception. It is well known that music makes us move, but these studies show that the act of feeling a rhythm is an interactive process: hearing a rhythm evokes physical movement and the resulting vestibular stimulation also influences the auditory interpretation of the rhythm. The lack of correlation between years of musical training and size of the vestibular influence on audition, in Fig. 5 – Results. Percentage of times subjects identified the ambiguous auditory pattern as duple for each of the four conditions. Open bars after stimulation at the duple frequency, shaded bars after stimulation at the triple frequency. Left pair of bars after galvanic stimulation of the vestibular system (see Fig. 3, left panel), right pair of bars after control stimulation of the elbows (see Fig. 3, right panel). The horizontal dotted line represents chance responding (50%). Error bars represent the standard error of the mean. 40 cortex 45 (2009) 35–43 Author's personal copy conjunction with previous findings of movement–auditory interactions in infants (Phillips-Silver and Trainor, 2005), suggests that vestibular influence on auditory processing might arise early in development and not depend on any special experience. The vestibular system is a very primitive system that emerges early in both phylogeny and ontogeny and that determines the organization and development of the other senses. Given the primal role of the vestibular system it is perhaps not surprising that it has such a fundamental influence on auditory perception. Phylogenetically the vestibular system was the first sensory system to develop in evolution (Walls, 1962) and ontogenetically it is the first system to develop in the womb (Romand, 1992), suggesting that a sense of orientation in the gravitational field is more fundamental to perception than is vision and hearing. Indeed vestibular experience appears to be fundamental even for social–emotional development in primates. Vestibular input through movement experience can partially ameliorate the detrimental effects of maternal separation in infant rhesus monkeys raised by cloth-covered surrogate mother cylinders (Mason and Berkson, 1975), as in Harlow's famous experiments (Mason and Harlow, 1958). An important role for the vestibular system, in addition to its fundamental role in providing orientation information, arises because it is dynamically sensitive in the range of biological rhythms, especially those in the frequency range of locomotion (Wilson and Jones, 1979). Biological rhythms are pervasive and exist at many different temporal scales. Two of the most likely sources of biological rhythm at the time scale of musical rhythm are locomotion and heart beat. The tempo range of locomotion movements corresponds closely to the range over which a beat can be felt – pulse separations of between about 300 and 900 msec (e.g., Fraisse, 1982; Clarke, 1999) and heart rate varies from about 60–150 beats/min, corresponding to a very similar range of 400–1000 msec. Both of these rhythms can be directly sensed by the vestibular system. The large physical motions associated with walking and running of course excite the vestibular system, but even the tiny movements of the head caused by the pulse are also detected (Crawford, 1952). Developmentally, both of these biological rhythms are experienced by the fetus as the mother locomotes through the environment. But at what stage of development, and where in the nervous system does vestibular input connect with auditory rhythmic experience? Although the auditory and vestibular end organs are anatomically close and functionally similar, sounds must be at least 95 dB before they directly stimulate the vestibular system (Todd and Cody, 2000). As the sounds in this experiment are much quieter than this, the auditory–vestibular interaction that we have demonstrated must occur more centrally. There is a potential concern that our galvanic stimulation might have had a direct

effect on the auditory portion of the VIII nerve (Bucher et al., 1998). However, this is very unlikely because the currents used were very small and none of our subjects reported hearing any sounds. The relevant auditory–vestibular interactions are more likely to occur more centrally. Recent evidence indicates that auditory and vestibular information may interact at many levels of the nervous system, including the dorsal cochlear nuclei (DCN) (Oertel and Young, 2004), and the posterior parietal cortex (PPC) (Bremmer, 2005; Colby et al., 1993; Lewald et al., 2002; Lewis and Van Essen, 2000; Schlack et al., 2005, 2002). Models of rhythmic movement have largely focused on interactions between PPC, cerebellum and prefrontal cortex (e.g., Todd et al., 2002). The cerebellum in particular has been implicated in the processing of auditory rhythm (Penhune et al., 1998; Parsons, 2003; Griffiths, 2003; but see Molinari et al., 2005). The cerebellum is a major recipient of vestibular input (e.g., Suzuki and Keller, 1982). The role of the cerebellum in timing has been conceptualized not as a clock or counter but simply as the structure that provides the necessary circuitry for the sensory systems to extract temporal information and for the motor system to learn to produce a precisely timed response (Penhune et al., 1998). The effect of vestibular stimulation of auditory rhythm, then, is likely to provide a similar enhancement to the auditory sensory signal on selected strong beats as would an increase in auditory intensity. The ventral intraparietal area (VIP) of the PPC is of particular interest as well because single cell recordings in the Macaque monkey show that it responds to both auditory (Schlack et al., 2005) and vestibular (Colby et al., 1993; Bremmer et al., 2001; Schlack et al., 2002) input as well as to visual and somatosensory stimulation. The view of the PPC as an integrator of acoustic and vestibular cues, together with evidence of area VIP as a site of multimodal neurons that code for spatial perception and self-motion, offers an account of the auditory–vestibular connections that may underlie our findings of multisensory interactions between movement and the perception of auditory rhythm (see Phillips-Silver and Trainor, 2008). The locus of vestibular–auditory interactions could be determined in a number of ways. fMRI studies comparing strengths of activation across different regions for auditory alone, vestibular alone, and combined auditory–vestibular stimulation would be informative. Studies of whether patients with lesions in different auditory–vestibular convergence sites experience the influence of vestibular stimulation on auditory rhythm processing would also give information about which brain regions are critical. Finally, if vestibular–auditory effects are cortically mediated, no multisensory effect would be expected in infants two months of age and younger, as the auditory cortex is not mature enough at this stage to support complex processing (Moore and Guan, 2002). 5. Conclusions Musical rhythm patterns elicit physical movement from head bobbing and foot tapping to all-out dancing. Our previous work showed that movement of the body can influence the auditory perception of the metrical structure of rhythm. The present paper demonstrates that this effect is mediated by vestibular stimulation and can be recreated in the absence of physical movement by artificially stimulating the vestibular nerve. Most likely, several regions of vestibular–auditory convergence are involved in some way in rhythm processing and it will be for future research to discover the specific role of each region. cortex 45 (2009) 35–43 41 Author's personal copy Acknowledgements This research was supported by grants from NSERC (Canada) to Laurel Trainor and Laurence Harris. We thank Jessica Phillips-Silver for discussions of the stimuli and Lisa Hotson for organizational assistance. references Arom S. African Polyphony and Polyrhythm. Cambridge: Cambridge University Press, 1991. Baruch C and Drake C. Tempo discrimination in infants. Infant Behaviour and Development, 20: 573–577, 1997. Bremmer F. Navigation in space- the role of the macaque ventral intraparietal area. The Journal of Physiology, 566: 29–35, 2005. Bremmer F, Schlack A, Duhamel J-R, Graf W, and Fink GR. Space coding in primate posterior cortex. Neuroimage, 14: S46–S51, 2001. Bridgeman B and Stark L. Ocular proprioception and efference copy in registering visual direction. Vision

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Abstract

To understand the contribution of the human presupplementary motor area (pre-SMA) in sequential motor behavior, we performed a series of finger key-press experiments. *Experiment 1* revealed that each subject had a spontaneous tendency to organize or "chunk" a long sequence into shorter components. We hypothesized that the pre-SMA might have a special role in initiating each chunk but not at other points during the sequence. *Experiment 2* therefore examined the effect of 0.5-s, 10-Hz repetitive transcranial magnetic stimulation (rTMS) directed over the pre-SMA. As hypothesized, performance was disrupted when rTMS was delivered over the pre-SMA at the beginning of the second chunk but not when it was delivered in

the middle of a chunk. Contrary to the hypothesis, TMS did not disrupt sequence initiation. *Experiments 3* and *4* examined whether the very first movement of a sequence could be disrupted under any circumstances. Pre-SMA TMS did disrupt the initiation of sequences but only when subjects had to switch between sequences and when the first movement of each sequence was not covertly instructed by a learned visuomotor association. In conjunction, the results suggest that for overlearned sequences the pre-SMA is primarily concerned with the initiation of a sequence or sequence chunk and the role of the pre-SMA in sequence initiation is only discerned when subjects must retrieve the sequence from memory as a superordinate set of movements without the aid of a visuomotor association. Control experiments revealed such effects were not present when rTMS was applied over the left dorsal premotor cortex.

INTRODUCTION

A fundamental aspect of human motor behavior is our ability to organize actions in a specific spatiotemporal order to achieve goal-directed behavior. The medial frontal cortex has been implicated in such sequencing of actions. Recent studies have particularly emphasized the sequencing role of the presupplementary motor area (pre-SMA), located in the rostromedial aspect of Broadmann's area 6, within the medial frontal region. Regional cerebral blood flow and blood oxygenation-level-dependent (BOLD) signals in the pre-SMA change when sequences are learned (Hazeltine et al. 1997; Hikosaka et al. 1996; Jenkins et al. 1994; Sakai et al. 1998, 1999) and lesions, pharmacological inactivation, or transcranial magnetic stimulation (TMS) in this area disrupt the performance of well-learned sequences (Chen et al. 1995; Gerloff et al. 1997; Halsband 1987; Muri et al. 1994, 1995; Shima and Tanji 1998a).

Pre-SMA cells modulate their activity when sequences are performed, but in many studies, such modulation is transient

and may only occur at certain points within a well-learned sequence (Nakamura et al. 1998; Shima and Tanji 2000; Shima et al. 1996). Nakamura et al. (1998) taught their monkeys ten movement sequences by teaching them a “hyperset” constructed from five pairs or “sets” of movements. These authors found extensive pre-SMA activity during the learning of a sequence. However, once a sequence was well learned, the activity of pre-SMA cells was greatly reduced, but any remaining pre-SMA activity was often confined to just the very first trial (or even the 1st set) of a well-learned hyperset. This suggests pre-SMA neurons are particularly interested in initiating sequences or component parts of sequences. Shima et al. (1996) similarly reported that many (25%) neurons in the pre-SMA fire in relation to just the first movement of a sequence. Moreover the firing pattern seemed to indicate a role in updating the sequence because the first movement-related activity was most prominent when the sequence changed and a new sequence had to be performed. Matsuzaka et al. (1996) also reported that many (31%) pre-SMA neurons fire when monkeys have to change and update a movement plan. Inactivation of the pre-SMA (Shima and Tanji 1998a) has demonstrated an essential role of the pre-SMA when a sequence is first retrieved from memory.

The more posterior SMA proper, together with the pre-SMA, may code for intervals between specific movements within a sequence and the rank order of sequence movements. Rank order and interval selective neurons are more prevalent in the pre-SMA and SMA, respectively, but both types of neuron are found in both areas (Shima and Tanji 2000). The pre-SMA, however, may be unique in making certain intermittent contributions to action sequences; it may be required when the sequence is first initialized, but subsequently it may only be of most importance at further points of higher level re-organization or re-direction of the sequence but not on the execution of every movement.

Reaction time (RT) analyses suggest that sequences exhibit two aspects of organizational structure. First, higher-level organizational processes are apparent when sequences are initiated. Before subjects make the first movement in a sequence, they are preparing aspects of the entire sequence of movements not just the first single movement. Sternberg et al. (1978) demonstrated that the RT of the first movement of a sequence increased as the total sequence length increased. It is possible that the prominent pre-SMA activity prior to the initiation of a sequence (Nakamura et al. 1998; Shima and Tanji 2000; Shima et al. 1996) is related to the process of sequence organization and initiation studied by Sternberg et al. (1978) rather than just the selection or execution of the first movement of the sequence.

A second aspect of sequence organization is sometimes apparent after the sequence is initiated. Several behavioral studies on sequence learning have suggested movement sequences are performed as if they consisted of subsequences or "chunks" (Koch and Hoffmann 2000; Nissen and Bullemer 1987; Perruchet and Amorim 1992; Povel and Collard 1982; Restle and Burnside 1972; Rosenbaum et al. 1983; Verwey 2001). The start of a chunk is indicated by a movement with a longer reaction time. In general, such investigations have imposed statistical or relational patterns (Koch and Hoffmann 2000) between the elements of a sequence such as repetitions of elements within the sequence, grouping elements of the sequence together by imposing pauses between certain elements, or transposing certain elements within a sequence. These imposed structure patterns have the effect of creating artificial "chunk points." Thus it is not clear whether humans will spontaneously organize a random sequence into groups or chunks in the absence of such statistical or relational structure patterns. Such spontaneous organizational patterns in random sequences have proven difficult to discern at the group level because of highly individual organizational strategies. Verwey et al. (2003) demonstrated

that at the group level, organizational patterns of sequences become more variable as the sequences become less structured. However, if such organizational strategies emerge as a genuine aspect of visuomotor sequence learning, possibly to overcome limitations of working memory, then it is possible that this process may also be under the control of the pre-SMA given its reciprocal connections with the prefrontal cortex (Bates and Goldman-Rakic 1993; Lu et al. 1994; Luppino et al. 1993).

Given the limitations of working memory (Miller 1956), *experiment 1* sought evidence for the spontaneous organization of long sequences of finger key-press movements into component units or chunks. We taught subjects a bimanual sequence of 12 alternating movements until they could perform the sequence from memory (Fig. 1). Such a long bimanual sequence was chosen for two reasons: a pilot study demonstrated that an eight-movement sequence does not necessitate organization of a sequence into subsequences and bimanual sequences (as opposed to unimanual sequences) increase the number of possible movements in a sequence, thus reducing statistical or relational structure patterns that could influence chunking. A consistent pattern of increased response time (RT) at one movement of the sequence (other than the 1st) was taken as evidence for the operation of a further process of sequence organization after initialization. We refer to such organizational features of sequences as “chunk points.”

fig. 1.
Subjects sat facing a computer monitor and made finger press sequences using an 8-key button press box where the buttons are numbered from left to right, with the left little finger button 1, the left index finger button 4, the right index finger button 5 and the right little finger button 8. Initially, subjects were taught these sequences using visual guidance (*left*). Nonmoving fingers were indicated by blue ellipses while a red ellipse instructed the proper move. The visual guidance of each movement continued for the entire sequence on a given trial. If a mistake was made during the sequence, a 100-Hz, 200-ms tone was sounded and the trial was stopped. The red ellipse remained to indicate the proper move and a green ellipse appeared over the finger position that

the subject actually pressed. In *trials 5–20,* visual guidance was pseudorandomly removed on some of the trials so that the subjects only saw a blank screen and had to perform the sequence from memory (memory guided) without visual guidance (*right*). All trials were memory guided after *trial 20.* Once subjects successfully completed 10 consecutive memory guided trials without error, experimental trials began.

In *experiments 2–4,* we sought to capitalize on the temporal specificity of transcranial magnetic stimulation (TMS) to investigate the role of the human pre-SMA at specific time points within a well-learned sequence. Single pulses or short trains of TMS transiently disrupt the normal pattern of activity in a cortical area for tens or hundreds of milliseconds, and behavioral performance is also disrupted and slowed if the brain area is essential for task performance (Jahanshahi and Rothwell 2000; Pascual-Leone et al. 2000; Walsh and Cowey 2000; Walsh and Pascual-Leone 2003). *Experiment 2* was designed in the same way as *experiment 1,* but now trains of 10-Hz repetitive TMS (rTMS) were applied over the pre-SMA just prior to the first movement, the chunk point, and the nonchunk point (a movement in the middle of a preorganized chunk). We predicted that the TMS would disrupt performance if applied when the sequence was initially organized (1st movement) or subsequently updated (chunk point) but not when it was applied at the nonchunk point. *Experiments 3* and *4* (Fig. 2) further explored the effect of pre-SMA TMS on the first movement of a sequence when subjects performed two short sequences with visual cues instructing which sequence to perform (*experiment 3,* cue-sequence task) or when visual cues instructed subjects to either repeat or switch sequences (*experiment 4,* cue–change task). To test the specificity of any disruptive effects of pre-SMA TMS, we also examined the effect of TMS applied over the dorsal premotor cortex (PMd). The control experiments focused on the left PMd because it has been shown to be dominant for movement selection (Johansen-Berg et al. 2002; Schluter et al. 1998).

fig. 2.

Top: a schematic indicating the appropriate action for each screen color for the cuesequence and -change tasks used in *experiments 3* and *4. Bottom*: these 2 panels indicate how the screen color cues the 1st movement of the sequence for each of the tasks. In cue sequence (*experiment 3*), each screen color is associated with a specific sequence. In the cue-change task (*experiment 4*), the screen color is not associated with a sequence but instead indicates whether to continue the same sequence as performed on the previous trial (pink screen) or to switch to the other learned sequence (yellow screen). Notice that in cue-change task the subjects are initially visually guided (*bottom, trial 1*) as to which of the 2 sequences to perform. After the visual guidance is removed (after *trial 3* but shown here only for *trial 1*), the subjects must recall which sequence was performed on the previous trial to then select the appropriate sequence for the current trial.

METHODS

General task

All of the experiments consisted of bimanual sequences of finger movements using an eight-button keypad, where the fingers are numbered from left to right starting with the left little finger as key 1 and the right little finger as key 8 (Fig. 1). Subjects nearly always alternated hands with each movement of a sequence, and each sequence was carefully designed to prevent statistical or relational structure patterns that may impose artificial sequence organization, i.e., runs, repetitions within consecutive or adjacent movements, transpositions, inversions, or mirroring of movements (see Keele et al. 1990; Koch and Hoffmann 2000 for reviews). An example of such statistical or relational structure would be a sequence of twelve movements such as 123-123-234-432, where elements 1–3 are a run; elements 4–6 are a repetition of elements 1–3; elements 7–9 are a transposition of elements 4–6; and elements 10–12 are an inversion of elements 7–9. Bimanual sequences were used (as opposed to unimanual sequences) to reduce statistical or relational structure patterns that could influence the subject group to chunk at a specific position in the sequence. To keep from introducing any new variables,

bimanual sequences were also used in the investigations of sequence initiation in *experiments 3* and *4.*

Subjects were seated facing a PC computer with their chin in an adjustable chin rest. Subjects were first given specific instruction about the task. Once the task had been explained, each subject was given a learning block. Sequence learning was initially aided by visual guidance (Fig. 1, *left*). Each trial of a sequence began with a 500-Hz warning tone that lasted 500 ms, followed by a 1-s delay before a 150-ms initiation tone was sounded. The eight different finger positions corresponding to the orientation of the hands on the eight-button keypad were then displayed on a colored screen. Blue ellipses defined seven of the finger positions and a red ellipse marked the finger to be pressed. After the subject pressed the appropriate finger, a 500-Hz, 200-ms correct tone was sounded. A blue ellipse then replaced the red ellipse, and a red ellipse appeared at a new finger position instructing the next movement of the sequence. This continued until the sequence was completed. Each complete sequence defined a trial. Response times for the first movement in the sequence were recorded from the illumination of the screen beginning the trial. Response times (or inter-response times) for movements after the first movement were recorded from the end of the previous movement's correct tone. If a mistake was made during the sequence, a 100-Hz, 200-ms error tone was sounded, and the trial was aborted. The red ellipse remained to indicate the proper move, and a green ellipse appeared over the finger position that the subject actually pressed. The first five learning trials were aided by visual guidance. In *trials 5–20,* visual guidance was pseudorandomly removed on some of the trials so that the subjects only saw a blank colored screen and had to perform the sequence from memory (memory guided) without visual guidance (Fig. 1, *right*). After *learning trial 20,* all of the trials were memory guided until the subjects could reach the criterion of 10 consecutive memory-guided trials without an error. Once this criterion was reached, the training block ended and the

subjects began memory-guided experimental blocks.

TMS procedures

All TMS pulses were generated by a Magstim Rapid TMS machine (Whitland, Whales, UK), with a maximum output of 2.0 T. The parameters used were within the previously established safety guidelines (Wassermann 1998) and were approved by the Central Oxford-shire Research Ethics Committee (Reference No. C99.178). All subjects were right-handed, healthy individuals with no history of head injury or seizure history within the family. Informed consent was obtained from all participants before participation.

pre-sma. We localized the pre-SMA site using a method previously reported (Hadland et al. 2001; Rushworth et al. 2002). We first localized the foot representation within each subject's motor cortex by using single-pulse stimulation along the midline starting at a point 2 cm posterior to Cz. Coil position was then adjusted in steps of 0.5 cm as the stimulation intensity was once again reduced to determine the maximally excitable foot representation in the motor cortex. The coil was then moved 6 cm anterior to stimulate the pre-SMA.

In previous studies, magnetic resonance image (MRI)-guided frameless stereotaxic confirmation of coil position had shown that moving the coil 5–6 cm anterior to the motor cortex placed it above the pre-SMA region (Hadland et al. 2001; Paus 1999; Rushworth et al. 2002). In the present study, coil positioning over the pre-SMA was confirmed by using the Brainsight frameless stereotaxy system (Rogue Research, Montreal Canada) for 10 subjects (12 localizations in total, see Fig. 3, *left*). For these subjects, a Polaris (Northern Digital, Waterloo, Canada) infra-red tracking system was used to measure the position of anatomical landmarks on each subject's head that are also visible on each MRI scan (nose tip, bridge of nose, left and right intra-trageal notches). Each subject's head and MRI were then co-registered, and another

infra-red tracker was used to monitor the position of the TMS coil with respect to the brain. Each subject's brain MRI was also registered to an average of 305 brains aligned with Talairach space (Collins et al. 1994; Talairach and Tournoux 1988), using Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library tools (FMRIB, Oxford, UK; www.fmrib.ox.ac.uk/fsl) so that TMS stimulation coordinates could be identified in standard space (Fig. 3, *left*). This method confirmed that in 10 of 12 cases subjects received TMS over the midline at or anterior to the vertical line (VAC line) through the anterior commissure at a position between y = -2 mm and y = 23 mm (group mean, y = 5.5 mm) at the approximate position of the pre-SMA (Picard and Strick 1996, 2001; Stephan et al. 1995; Vorobiev et al. 1998). There was a slight tendency for the TMS site to be biased toward to the left hemisphere (group mean coordinate x = -5.1, shown as slice x = -7 in Fig. 3, *left*). This may reflect a lateral bias introduced while localizing the foot motor hot spot, which tends to be just off midline. Our previous experiments have all suggested dominant roles for left hemisphere motor areas (Johansen-Berg et al. 2002; Rushworth et al. 2001, 2002; Schluter et al. 1998).

fig. 3.
Composite image of the locations where transcranial magnetic stimulation (TMS) was applied for the presupplementary motor area (pre-SMA, *left*) and the dorsal premotor cortex (PMd, *right*) sites. Sections taken at the group average sagittal plane. Dashed line denotes y = 0.

All pre-SMA TMS experiments used 10-Hz, 5-pulse rTMS trains at 110% of each subject's individually determined active motor threshold. Stimulation was applied with a Magstim “cone” coil in a similar manner to previous TMS investigations of medial frontal cortex (Hadland et al. 2001; Harmer et al.

2001; Rushworth et al. 2002).

pmd. In the series of control experiments, TMS was directed over the left PMd. The PMd site was localized using a method previously reported (Johansen-Berg et al. 2002; Praamstra et al. 1999; Rushworth et al. 2002; Schluter et al. 1998, 1999). We first localized the hand representation within each subject's motor cortex by using single pulse stimulation starting at a point 2 cm anterior and 4 cm lateral to Cz. The stimulation strength began at 40% of stimulator output and was increased in steps of 5% until a just visible twitch was seen in the right hand while subjects were instructed to spread their fingers using 10% of maximum force. Coil position was then adjusted in steps of 0.5 cm as the stimulation intensity was once again reduced to determine the hot spot.

The coil was then moved 2 cm anterior and 2 cm medial to the motor cortex hot spot to stimulate PMd. The coil was adjusted to a slightly more anterior and medial position if TMS pulse trains at experimental parameter levels caused visible motor twitches. In previous studies, MRI-guided frameless stereotaxic confirmation of coil position had shown that moving the coil to this position placed it above the superior branch of the superior precentral sulcus in the approximate vicinity of PMd (Johansen-Berg et al. 2002; Paus 1999; Rushworth et al. 2002). In the present study, coil positioning over the PMd was confirmed for 12 subjects (15 localizations in total, see Fig. 3, *right*) by using MRI guided frameless stereotaxic localization as described in the preceding text. Coil placement over the PMd was confirmed (group mean: x = -28.7 mm, y = 6.8 mm, z = 67.0 mm).

All PMd TMS experiments used 10-Hz, 5-pulse rTMS trains at 110% of each subject's individually determined active motor threshold to elicit a twitch of the fingers. Stimulation was applied with a Magstim 70 mm “figure 8” coil in a similar manner to previous TMS investigations of PMd (Johansen-Berg et al. 2002; Praamstra et al. 1999; Rushworth et al. 2002;

Schluter et al. 1998, 1999).

fig. 8.
First movement RT data for the cue-sequence task in *experiment 3.* Pre-SMA TMS (*A*) or PMd TMS (*B*) did not disrupt the initiation of a sequence.

Subjects

In total, 32 subjects participated in the series of four experiments that were conducted over an 18-mo period. Testing was not completed for one subject, who found the PMd TMS uncomfortable, and there was insufficient data for analysis. In total, 54 subject data sessions were gathered and form the basis of this report. Some subjects participated in more than one experiment. For this reason, the sequence changed between TMS sites and between experiments to avoid practice effects. Thus within an experiment, the sequence in a pre-SMA group remained the same for all subjects but differed from the sequence performed by the PMd group. No more than two subjects ever participated as subjects within both TMS groups of the same experiment, and subjects never received TMS at both sites within the same testing session. Although the order of experiments was not randomized (the design of later experiments was determined by the results of the earlier experiments), there were long intervals of weeks or months between experiments while results were analyzed, new tasks were designed, and subjects had MRI scans. Details of each sequence are given in the following text.

All subjects were naïve to the purpose of the chunking experiments, and no indication was given to the subject that organizational strategy in movement was the focus of the study. Two of the authors took part as subjects in *experiment 3* and

one of the authors participated in *experiment 4.* Analyses of the data both with and without the authors' data always lead to similar outcomes.

Analysis

TMS disruption is transient, and RT increases, rather than error increases, have proven to be sensitive indices of behavioral performance (Bestmann et al. 2002; Campana et al. 2002; Johansen-Berg et al. 2002; Praamstra et al. 1999; Rushworth et al. 2002; Schluter et al. 1998, 1999; Walsh and Cowey 1998; Walsh et al. 1998). Therefore as in previous TMS experiments, analysis focused on RT increases. However, because high-frequency TMS over the more caudal medial premotor cortex has previously been shown to induce sequencing errors (Gerloff et al. 1997), an analysis of error rates was performed, but TMS did not significantly influence error rates in any of the present experiments, and therefore error rates will not be reported. For simplicity, the term “RT” will be used as a convention, even when referring to response times of movements after the first movement. For each subject, we calculated the median RT and error rate for each sequence position for all of the repetitions of that sequence. These median scores for each movement position and each subject were then analyzed using repeated-measures general linear models (GLMs), using within-subject correction procedures (Huynh-Feldt) where appropriate. A group mean of the individual median RTs or error rates for each subject was then calculated and reported in all cases unless otherwise specified. When necessary, the interpretation of significant interaction effects was aided by one tailed paired sample *t*-test.

Experiment 1: behavioral chunking

This experiment was performed to examine how subjects represent long sequences of actions and to see whether there is a tendency to divide a long sequence of movements into smaller component chunks.

subjects. Eight subjects performed this task (6 female, 2 male). Subjects were between 21 and 25 yr of age and all were right handed.

task. Subjects performed a bimanual sequence of 12 finger movements (617428362753). Subjects were first trained on the sequence as previously described. Once criterion was reached during the training block, three blocks of 20 memory-guided trials were performed with an inter-trial interval of 4.5 s. Subjects were cued to initiate a trial by the appearance of a yellow screen and an 800-Hz initiation tone. During the inter-trial interval, subjects saw only a black screen. Once all three experimental blocks were finished, the data were examined for the existence of chunking.

Experiment 2: chunking task with TMS applied over the pre-SMA or PMd

The main objective of this experiment was to examine whether 10-Hz rTMS over the pre-SMA or left PMd disrupted the performance of a sequential button-pressing task when applied at different time points during the sequence. Three stimulation points were examined: the first movement of the sequence; the "chunk point," the movement with the highest RT within the sequence indicative of the initiation of a new chunk; and at the nonchunk point, a low-RT movement in the middle of a chunk.

subjects. Fourteen subjects performed this task (11 male, 3 female; 7 subjects in each TMS group). Subjects were between 23 and 40 yr of age and all were right handed.

task. The experimental stimuli and design were the same as in *experiment 1,* but the actual sequences differed (pre-SMA group: 257361742835; PMd group 471526382746). Subjects were first trained on the sequence as previously described. Once criterion was reached during the training block, a memory-guided behavioral block of 20 trials was performed. This block was used to assess the location of each subject's

chunk point and nonchunk point on the basis of an immediate median RT analysis. The chunk and nonchunk points were always separated by at least three other intervening movements and the nonchunk point could never be the last movement of the sequence. The task program was then adjusted so that TMS trains could be administered according to a pseudorandom design on 35% of the trials of the first movement of the sequence, the chunk point movement, and the nonchunk point movement. Each subject then performed two blocks of 30 memory-guided trials with TMS applied at any of the three stimulation points. TMS at the first movement point occurred at the offset of the 800Hz initiation tone. TMS at both the chunk or nonchunk points occurred immediately after the subject completed the movement preceding either point.

Experiment 3: cue–sequence task with TMS applied over the pre-SMA or PMd

This experiment was designed to examine whether the first movement of a sequence might be more susceptible to TMS induced disruption if subjects were required to switch between two short sequences. Subjects were taught two sequences, and on each trial they were instructed to initiate a sequence by the presentation of one of two easily identifiable sensory cues.

subjects. Fourteen subjects performed this task (12 male, 2 female; 8 subjects in pre-SMA group, 6 subjects in PMd group). Subjects were between 19 and 36 yr of age and all were right handed. Three subjects (2 male, 1 female, ages 23–34), all right handed, performed a second control experiment.

task. Subjects performed two bimanual sequences of five nonrepeating finger movements. Subjects were taught two cue-sequence associations. They were told to perform *sequence A* (pre-SMA group: 73516; PMd group: 61738) when they saw a pink background and heard a 200-Hz initiation tone and to perform *sequence B* (pre-SMA group: 38462; PMd group: 46283) when they saw a yellow background and heard an 800-

Hz initiation tone. Subjects were then given a practice block with both sequences randomized over the block using the learning criterion previously described. After completion of 10 consecutive trials without error, the training block was terminated and two blocks of 30 memory-guided trials were performed. The two different sequences were pseudorandomly generated across these two blocks with TMS pseudorandomly applied on 50% of the trials at the offset of the initiation tone. In a subsequent control experiment to investigate the importance of the precise onset of the 500-ms TMS train, we applied the first pulse of TMS over the pre-SMA at the onset of the initiation tone.

Experiment 4: cue-change task with TMS applied over the pre-SMA or PMd

The cue-sequence task used in *experiment 3* was intended to employ an association between cues and sequences. There were also, however, inadvertent associations between each cue and the first movement of each sequence. For example, not only was the pink screen color and low pitched tone associated with *sequence A,* but it was also consistently associated with the first movement of *sequence A,* whereas the yellow screen color and high pitched tone was not only associated with *sequence B,* but also with the first movement of *sequence B. Experiment 4* was designed to examine the effect of TMS on the retrieval of movement sequences in the absence of the confounding effect of cue-first movement associations. In *experiment 4,* subjects were once again taught two sequences, and once again they were required to alternate between them. Now, however, the visual cues presented at the beginning of each trial simply instructed subjects to repeat the previous sequence or to switch to the other sequence. In this way, it was ensured that no simple cue-first movement associations could operate. As is shown in the following text, the change in behavioral context clearly altered the way the task was performed and the sequence initiation RTs were affected. To approximately equate the average movement

initiation RT in the present experiment with that used in *experiment 3,* we taught subjects a slightly longer bimanual sequence of six movements.

subjects. Fifteen subjects performed this task (13 male, 2 female; 8 subjects in pre-SMA group, 7 subjects in PMd group). Subjects were between 22 and 33 yr of age and all were right handed.

task. Subjects performed two bimanual sequences of six nonrepeating finger movements (pre-SMA group: 284637, 527163; PMd group: 351726, 735284). The experimental stimuli were similar to the previous experiments. Subjects were told they were to perform two different sequences and that whenever they saw a pink screen, they were to repeat the same sequence as they had performed on the previous trial, and whenever they saw a yellow screen, they were to switch to the other sequence they had learned (Fig. 2). Switch trials occurred every four to seven trials, although subjects were only told they would never have to switch on successive trials.

Subjects were first trained on each sequence separately. The screen color for each of the sequences during training was blue. Once they could perform each sequence to criterion, they were given a practice block of the experimental condition. Both the practice and experimental blocks began with visual guidance of the same sequence for the first three trials. Because there were no sensory cues to guide sequence selection, visual guidance was needed at the very beginning of a block to inform the subjects which sequence to continue performing (Fig. 2, *bottom*). On *trial 4,* the visual guidance disappeared, and subjects only saw a pink screen and had to recall which sequence they performed on the previous trial to select the correct response on the current trial. Once a yellow screen appeared, subjects were required to switch to the other sequence. After completion of 10 consecutive trials without error, the training block was terminated and an experimental block was performed. Each trial was initiated with an 800-Hz,

150-ms tone, and the inter-trial interval was 3.5 s. TMS was pseudorandomly applied on 50% of the switch trials and 20% of the repeat trials. Because of the pseudorandom design, each subject performed enough trials to get ≥10 data points for each of the four possible conditions: TMS-switch, no TMS-switch, TMS-repeat, no TMS-repeat. This meant the number of trials each subject performed varied between 100 and 200 trials for each of the TMS locations. TMS was applied at the onset of the initiation tone.

RESULTS

Experiment 1: behavioral chunking

The performance of an example subject in each of the three blocks of 20 repetitions of the sequence is shown in Fig. 4. The first movement of the sequence is characterized by a long RT that indexes the planning and organizing of the upcoming sequence rather than the difficulty of selecting a particular movement (Sternberg et al. 1978). There is, however, an additional clear increase in RT on the eighth movement indicating the updating and reorganization of the sequence at this point. The sequence is divided into two chunks of seven and five movements by this subject, and this pattern of chunking appears to be stable throughout three testing blocks. The long RT on the eighth movement is an example of what we refer to as a chunking point. This subject's chunk point was, on average, 229 ms slower than the subject's next slowest movement.

fig. 4.
An example of behavioral chunking in 1 subject's data from *experiment 1.* Data from each of the 3 blocks of 20 repeated trials are shown separately. Long response times (RTs) on the 1st movements of sequences has been taken to indicate the planning of the upcoming sequence. There is, however, an additional clear increase in RT on the 8th movement, indicating the updating and reorganization of the sequence at this point. The sequence appears to be divided into 2 chunks of 7 and 5 movements. It is also noticeable that the position of the chunking point remained constant across all 3 testing blocks.

When all subjects' data were averaged, there was a suggestion (Fig. 5*A*) of a general increase in RT on movements seven through nine, but a clear and uniform chunk point was difficult to discern at the group level. It was possible, however, to re-plot the data with respect to the longest RT for each subject (Fig. 5*B*). For example, the data for the individual subject shown in Fig. 4 would be re-plotted with respect to the eighth movement, which would be labeled point 0. The 9th and 10th movements would be re-labeled points 1 and 2, whereas the 6th and 7th movements would be re-labeled points -2 and -1, respectively. As expected, inspection of Fig. 5 (*right*) reveals the re-emergence of a chunk point at the group level after this reordering process. The RTs at the different points are now significantly different from one another [$F(3.01,15.06) = 4.97$, $P = 0.014$] and the chunk point RT at point 0 is significantly longer than either of the adjacent RTs ($P < 0.05$). Importantly each subject's re-ordering protocol from the first block (Fig. 5, *A* and *B*) can be applied to data gathered in the second block (Fig. 5*C*) or third block (Fig. 5*E*) and the chunk point reemerges (Fig. 5, *D* and *F*). Again in each case, the chunk point RT in each set is significantly longer than either of the adjacent RTs. In brief, although the chunking point varied between subjects, it remained at a consistent position within the sequence for a given subject.

fig. 5.

Left: group mean sequence performance RT data during 3 blocks, each of 20 trials, of the 12 movement sequence (*experiment 1*). The 1st, 2nd, and 3rd repetitions are shown at the *top, middle,* and *bottom.* The chunk point cannot easily be discerned in the data after group averaging (*left*). *B*: data from the 1st block, the same data as in *A,* after re-plotting with respect to each subject's trial with the longest RT (the chunk point). The chunk point is labeled movement 0. The 1st and 2nd movements after the chunk point are labeled 1 and 2, whereas the 1st and 2nd movements before the chunk are labeled -1 and -2. The chunk point significantly (* $P < 0.05$) re-emerges in the data for the 1st, 2nd, and 3rd blocks (*B, D,* and *F*).

Closer inspection of the data suggested clear evidence of chunking in six of the eight subjects (at mean sequence position: 7.83 ± 0.40 SE). For these six subjects, the chunk point RTs were on average 245 ± 70 (SE) ms slower than the next slowest movement once the first movement was excluded. The evidence for one subject appeared more equivocal. In one case, there was a suggestion of two chunk points as if the sequence were being divided into three chunks.

Experiment 2: chunking task and the effects of pre-SMA or PMd TMS

The subjects demonstrated clear and similar chunking effects during the behavioral sessions in both the pre-SMA and PMd experiments. The mean chunk point RTs were 681 ± 145 (SE) and 402 ± 111 (SE) ms, and the mean nonchunk point RTs were 171 ± 41 (SE) and 156 ± 32 (SE) ms in the pre-SMA and PMd groups, respectively (Figs. 6 and 7). The mean sequence positions where TMS was applied were 7.14 ± 0.67 and 6.71 ± 0.87 for the chunk points and 6.14 ± 1.26 (SE) and 7.29 ± 1.08 (SE) for the nonchunk points in the pre-SMA and PMd groups, respectively.

fig. 6.

Pre-SMA group RT data for the 3 different stimulation points in *experiment 2.* Pre-SMA TMS applied at the initiation of a chunk (chunk point) significantly slowed performance by 68 ms (* $P < 0.05$). No similar disruption was seen when TMS was applied at the nonchunk point or first movement of the sequence.

fig. 7.

PMd group RT data for the 3 different stimulation points in *experiment 2.* PMd TMS did not disrupt performance at any of the 3 stimulation points in the sequence.

The data were analyzed with a three factor GLM (3 levels of point: 1st movement, chunk point, nonchunk point; 2 levels of TMS: control, TMS; 2 levels of group: pre-SMA, PMd). The data for one subject who had participated in both pre-SMA and PMd groups were removed so that a between subject approach could be used to compare the two TMS groups. The absence of any main effect of group ($P > 0.1$) suggested that both groups were performing the sequences in a similar way. Likewise an analysis of just the baseline non-TMS trials confirmed the similarity of the performances of the two groups; again there was no main effect of group ($P > 0.1$). There was a two-way quadratic interaction between point and TMS [$F(1,10) = 9.65$, $P = 0.011$], consistent with the TMS having a different effect when it was delivered at one of the three points within the sequence. Moreover, the effect was modulated by the site of TMS; there was a three-way quadratic interaction among point, TMS, and group [$F(1,10) = 10.11$, $P = 0.010$]. Subsequent one-tailed linear contrasts showed that TMS had a significantly different effect when it was delivered at the chunk point depending on whether it was delivered over the pre-SMA or the PMd [$F(1,10) = 3.80$, $P = 0.040$] but not when it was delivered at the time of the first movement or the nonchunk point ($P > 0.1$). The analyses suggest that TMS only had a disruptive effect when it was delivered over the pre-SMA and only when it was delivered at a chunk point.

The interpretation was confirmed by a subsequent analysis of just the data from the pre-SMA group. There was a significant interaction between movement position and TMS [$F(1.92,11.50) = 4.03$, $P = 0.048$], suggesting that the disruptive effect of pre-SMA TMS depended on the time of its application. Pre-SMA TMS significantly slowed RT at the chunk point [$t(6) =$

2.16, $P = 0.038$], from a mean of 290–358 ms but not when it was applied at the first movement or the nonchunk point (Fig. 6). No such effects were apparent in a separate analysis of PMd TMS (Fig. 7).

It might be argued that the temporal relationship between pre-SMA TMS and movement is confounded when the chunk and nonchunk points are compared; by definition, the chunk point movement has a longer RT than the nonchunk point movement and the pulse train might not have finished before the nonchunk movement was made. The movements that follow the designated nonchunk movement, however, do stand in the same temporal relationship to the TMS as is the case for chunk movements. We therefore examined the effect of pre-SMA TMS on the first and second movements after the nonchunk movement. Not only did pre-SMA TMS not have any significant disruptive effect at the nonchunk point [$t(6) = 0.36$, $P > 0.05$], but it also had no significant disruptive effect on either the first [$t(6) = 0.92$, $P > 0.05$] or the second [$t(5) = 1.17$, $P > 0.05$] movement after the nonchunk movement.

Experiment 3: cue-sequence task and the effects of pre-SMA or PMd TMS

The data were analyzed with a three factor GLM (2 levels of switch: switch sequence vs. repeat sequence; 2 levels of TMS: TMS vs. control non-TMS; 2 levels of group: pre-SMA vs. PMd group). The two subjects who had participated in both TMS groups of *experiment 3* were removed from the pre-SMA group to maintain the highest statistical power. The absence of any main effect of group ($P > 0.1$) suggested that both groups were performing the sequences in a similar way. Likewise an analysis of just the baseline non-TMS trials confirmed the similarity of the performances of the two groups; again there was no main effect of group ($P > 0.1$). The analysis, however, revealed no differences in the effect of pre-SMA or PMd TMS on the first movement RT. Subsequent analysis of just the pre-SMA data (Fig. 8*A*) or just the PMd data (Fig. 8*B*) confirmed the

absence of any effect of TMS on first movement RT. It was noted in both pre-SMA and PMd groups that, surprisingly, subjects showed no RT cost of having to switch sequence.

Although TMS did not disrupt performance of the first movement, it was apparent that pre-SMA TMS slowed RTs on subsequent movements (Fig. 9*A*). A post hoc analysis of the individual RTs after the first movement (*movements 2–5*) revealed a significant slowing of RT when pre-SMA TMS was applied [$F(1,7) = 8.52$, $P = 0.022$]. By summing the individual RTs for each sequence, a measure of total sequence time (TST) was calculated. Despite the lack of a pre-SMA TMS effect on the first movement, TST (Fig. 9*A*) was significantly slowed on pre-SMA TMS trials [$F(1,) = 65.29$, $P < 0.001$]. As can be seen in Fig. 9*A*, pre-SMA TMS application slowed total sequence time by 91 ms on switch trials and 211 ms on repeat trials. Such a pattern of results suggested that the first movement was somehow preserved from the disruptive effect of the pre-SMA TMS, whereas future movements were not. No such effects were observed in a similar post hoc analysis of the PMd data. (Fig. 9*B*). Two possible interpretations of the pre-SMA TMS effect were tested. First, we investigated whether the TMS was being applied slightly too late to affect the first movement. In a control experiment, we applied the first pulse of the 500-ms pre-SMA TMS train 150 ms earlier, at the onset rather than the offset, of the initiation tone. Even in a small group of three subjects the same pattern of results was clear. Pre-SMA TMS never caused any disruption on the first movement (pre-SMA TMS made all 3 subjects faster on both switch and repeat trials) of the sequence, but the individual RTs of subsequent movements (*movements 2–5*) were significantly slowed [$F(1,2) = 57.17$, $P = 0.017$]. The second possibility, that the type of cueing used to instruct the sequences was the critical determinant of whether a first movement deficit would be found, was tested in *experiment 4.*

fig. 9.
Total sequence time data for the cue-sequence task in *experiment 3. A*: pre-SMA TMS significantly slowed (*$P < 0.05$) the total time required to complete the sequence. *B*: PMd TMS did not significantly disrupt total sequence time.

Experiment 4: cue-change task and the effects of pre-SMA or PMd TMS

A between-subject GLM analysis, similar to that used in *experiment 3,* was conducted on the first movement RTs. The two subjects who had participated in both TMS groups of *experiment 4* were each assigned to just one group. Unlike in *experiment 3,* there was a significant main effect of switch [$F(1,11) = 43.86$, $P < 0.001$], a significant interaction between TMS and switch [$F(1,11) = 5.17$, $P = 0.044$], and a three-way interaction among TMS, switch, and whether subjects were in the pre-SMA or PMd group [$F(1,11) = 6.06$, $P = 0.032$].

A separate analysis of just the pre-SMA data (Fig. 10*A*) confirmed that pre-SMA TMS significantly slowed RT on the first movement [$F(1,7) = 7.94$, $P = 0.026$]. Control RTs increased from a mean of 445 ms when the sequence repeated to a mean of 810 ms when the sequence switched. When TMS was delivered, the RTs increased to 580 and 942 ms, respectively. Such an analysis of just the PMd data (Fig. 10*B*) did not suggest that PMd TMS had the same disruptive effect. There was an interaction between the effect of TMS and the switching of sequence [$F(1,6) = 8.10$, $P = 0.029$], but subsequent analysis revealed no indication of a significant slowing in the RT of the first movement with TMS application. Instead the interaction was due to subjects being faster on switch trials when PMd TMS was applied (874 ms) as opposed to switch trials without TMS application (1,046 ms). On repeat trials, subjects were nonsignificantly slower on TMS trials (661 ms) than on non-TMS trials (568 ms).

fig. 10.
First movement RT data for the cue-change task in *experiment 4. A*: pre-SMA TMS significantly slowed (*$P < 0.05$) the initiation of a sequence. *B*: PMd TMS did not significantly disrupt the initiation of a sequence.

The total sequence times (TSTs) were also measured as in *experiment 3.* Because TMS was associated with an outlying, very high TST for one subject in the pre-SMA group (3,905 ms as opposed to a mean of 1,303 ms for the remaining 7 subjects), a logarithmic transformation was applied to the data prior to analysis. There was a significant disruptive effect of TMS [$F(1,11) = 6.44$, $P = 0.028$] and a significant effect of switching [$F(1,11) = 50.84$, $P < 0.001$] on TST, but no TMS by group interaction was present ($P > 0.1$). However, further analysis revealed that the disruptive effect of TMS on TST was significant [$F(1,7) = 7.97$, $P = 0.026$] in the pre-SMA group (Fig. 11*A*) but not in the PMd group ($P > 0.1$, Fig. 11*B*). When pre-SMA TMS was applied, TSTs increased from 836 and 1,365 to 1,042 and 1,629 ms on repeat and switch trials, respectively.

fig. 11.
Total sequence time data for the cue-change task in *experiment 4. A*: pre-SMA TMS significantly slowed (*$P < 0.05$) the total time required to complete the sequence. *B*: PMd TMS did not significantly disrupt total sequence time.

Re-analysis of chunking data

After obtaining three sets of data from the chunking tasks (*experiments 1* and *2*), it was possible to carry out a more

extensive analysis to identify factors that might have influenced chunking. We categorized each possible movement or movement transition in terms of the hand used (dominant, right hand or subdominant, left hand), the finger used (index, middle, or ring: there were insufficient little finger movements for analysis), and the distances between consecutive movements (the movement transitions were divided into 2 approximately equal-sized categories of near and far distances in which consecutive movements were 2–4 or 5–6 finger positions apart). Pearson's χ^2 tests were then used to test if the observed frequencies of chunking in each type of category differed from the expected frequencies. There was no significant effect of hand [χ^2 (1, $n = 20$) = 0; $P > 0.05$], finger [χ^2 (2, $n = 20$) = 1.82; $P > 0.05$], or inter-movement distance [χ^2 (1, $n = 20$) = 0; $P > 0.05$]. Chunking was not simply just associated with movements that involved transitions between the two hands. The hand used changed with nearly every movement of each sequence, but chunking patterns remained stable while a subject performed a sequence. The expected frequency of chunking in the absence of a hand transition was, therefore, too low to be analyzed. It was, nevertheless, noted that the observed and expected frequencies of chunking were consistent when movements were categorized on the basis of hand transition.

DISCUSSION

Organization of movement sequences into chunks

Experiment 1 demonstrated that subjects exhibit a spontaneous tendency to organize long sequences of actions into component chunks. As previously noted (Sternberg et al. 1978), the RT of the first movement of a sequence tended to be longer than subsequent RTs. It has been argued that the long RT does not reflect the difficulty of selecting the first movement of the sequence, but rather it is an index of retrieval and preparation of the whole sequence of movements. Later in the sequence, between approximately the seventh and ninth

positions in the sequence, there was a second increase in RT of, on average, 245 ms compared with the next slowest movement (other than the very 1st movement). We refer to this movement as the chunk point because the sequence appears to be divided into two component chunks at this position. Although the chunk point occurred at a constant position for any given subject throughout testing, its position varied between subjects (see Figs. 4 and 5). Hand dominance, transitions between hands, distances between the fingers used in consecutive movements, and finger identity did not provide any simple account of chunking patterns. Although it may be possible for such factors to influence chunking, they did not do so in the present experiments where nearly every movement transition involved an alternation of the hand. Such a variety of chunking patterns suggests that the chunking phenomenon is not simply the consequence of a particular movement transition that is physically difficult for all subjects to perform but rather reflects an organizing principle for the performance of a sustained motor program; part way through the sequence there appears to be a need to update the organization of the sequence and to retrieve the final chunk of movements. The timing of the chunk point, at approximately the seventh to ninth movement of the sequence, suggests that it may be related to the limited capacity of short-term memory stores (Miller 1956).

There have been previous claims of structured representations in movement sequences but these have tended to depend on presenting subjects with highly structured sequence instructions and then observing the degree to which the instructed structure is preserved during performance (Keele et al. 1990; Koch and Hoffmann 2000; Nissen and Bullemer 1987; Povel and Collard 1982; Rosenbaum et al. 1983). For example, subjects have been taught short three movement sequences and then longer sequences that could be decomposed into the previously taught short sequences (Verwey 2001). Long RTs have been observed at the transition points between the structured components in such

experiments. The structured representation of the sequence in the present experiment emerged spontaneously in the absence of any specific instruction or artificial imposition (runs, repetitions, inversions or transpositions) and in a slightly varying way for each subject. Moreover similar results were observed in *experiment 2,* with different sequences, when the effect of TMS was examined in the context of chunking (Figs. 6 and 7).

Role of the pre-SMA in updating sequence chunks

The role of the pre-SMA in updating sequence chunks was tested in *experiment 2* by the application of 0.5-s 10-Hz rTMS trains at either the chunk point or in the middle of a chunk at a position referred to as the nonchunk point. As predicted, pre-SMA rTMS disrupted performance, causing significantly longer RTs when it was applied at the chunk point at the initiation of a new sequence chunk but not when it was applied during the course of an ongoing chunk at the nonchunk position (Fig. 6). No disruptive effect of TMS was seen when it was applied over PMd, a control site also within the motor system (Fig. 7). This is consistent with the results of previous studies that have suggested a lesser involvement of the more lateral premotor cortex in action sequences (Chen et al. 1995; Mushiake et al. 1991).

It might be argued that the absence of a TMS effect at the nonchunk point is due to it taking some time for the effect of the TMS to accumulate and become disruptive, and RTs were, by definition, shorter at the nonchunk position. Because the nonchunk point had a control RT of 160 ms and the TMS train would not have been completed by this time, we examined the effect of TMS on the following two movements. Post hoc tests confirmed that no disruption to the two movements after the nonchunk point was induced by pre-SMA TMS. Moreover, a comparison of Figs. 6, 8, and 10 demonstrates that the susceptibility of a sequence's initial movement to being disrupted by pre-SMA TMS was not a function of its RT. Initial

sequence movements with comparatively short RTs (445 ms) in *experiment 4* were disrupted by pre-SMA TMS, whereas initial sequence movements with longer RTs in *experiments 2* and *3* (579 and 695 ms) were unaffected by pre-SMA TMS. In summary, the application of pre-SMA TMS at the chunk point caused an immediate disruption to performance, but it did not disrupt performance at the nonchunk point or any of the movements that immediately followed the nonchunk point.

Hikosaka and colleagues (Hikosaka et al. 1995; Nakamura et al. 1998; Rand et al. 1998, 2000) taught their monkeys long sequences of 10 movements by teaching them series of five short 2-movement sequences or sets. They referred to the entire 10-movement sequence as a hyperset. It is possible that each set within the hyperset could be likened to a chunk in the present experiment. Most of the neurons in the pre-SMA that were preferentially active in relation to the new learning of sequences were active on just the first movement of each set. On well-learned hypersets, there was little pre-SMA activity apart from the first trial or even first set at a time when the monkey had to discard one hyperset and retrieve and organize a different hyperset (Nakamura et al. 1998). The pattern of behavioral interference when TMS was applied at chunk points, but not at nonchunk points, might be predicted from the intermittent pattern of pre-SMA single neuron activity during the course of sequence performance.

At the chunk point, subjects have to update their current action plans. Matsuzaka and Tanji (1996) have reported activity in the pre-SMA specifically related to the changing of an action plan. They trained monkeys to respond to one of two targets and found 31% of pre-SMA neurons were active when the response involved a shift away from the movement made on the previous trial. Within the medial frontal cortex such responses were most prominent in the pre-SMA rather than in the SMA. Shima et al. (1996) taught monkeys several three-movement sequences. The monkeys performed a given sequence for 11 repetitions

and were then guided through performance of another sequence. They reported that 25% of pre-SMA neurons were most active at the transition between one sequence and the next. It could be argued that the transition between one movement chunk and another in the present experiment involves a similar change in current action plans.

The chunk sizes in the present experiment (mean sequence position: 7.14 ± 0.67) seem to reflect the constraints of working memory capacity for a limited number of items (Miller 1956). The anatomical connections of the pre-SMA mean that it is ideally situated to retrieve and update motor plans as working memory is, in turn, updated. The pre-SMA has reciprocal connections with the prefrontal cortex (Bates and Gold-man-Rakic 1993; Lu et al. 1994; Luppino et al. 1993), which has been implicated in working memory (Goldman and Rosvold 1970), as well as connections with the SMA, which projects to M1 and the spinal cord (Dum and Strick 1991, 1996; He et al. 1995). BOLD signal responses in the pre-SMA are modulated by working memory demands even if disruption of the area does not produce straightforward working memory deficits (Hadland et al. 2001). Both the pre-SMA and the prefrontal cortex are active when subjects are learning new motor tasks (Gomez Beldarrain et al. 2002; Jueptner et al. 1997; Nakamura et al. 1998; Robertson et al. 2001; Sakai et al. 1998, 2002; Toni et al. 1998), although of these two structures, the prefrontal cortex may have a dominant role in implicit procedural learning (Pascual-Leone et al. 1996; Willingham et al. 2002).

Activation within the prefrontal-pre-SMA circuit during learning might reflect the organization and refinement of the task into manageable chunks. Bor et al. (2003) have shown that lateral prefrontal activity increases when it is possible to organize task information into chunks. Anterior premotor regions, such as the pre-SMA and anterior parts of PMd, may then be important when the information in working memory is translated into a program for action (Ohbayashi et al. 2003).

Role of the pre-SMA in first initiating a sequence of movements

Contrary to initial predictions, pre-SMA TMS had no disruptive effect when it was applied before the very first movement in the sequence in *experiment 2* when the first sequence chunk was retrieved and prepared. Although many pre-SMA neurons are responsive during the new learning of sequences, those that remain active after learning tend to fire at the beginning of the sequence (Nakamura et al. 1998). A further series of experiments (*3* and *4*), however, demonstrated that pre-SMA TMS did disrupt the initiation of a sequence but that this disruption could only be detected after removing the influence of confounding variables as discussed in the following text. Control experiments demonstrated that TMS over PMd never affected sequence initiation.

There are several reasons for thinking that the first movement in *experiments 2* and *3* might have been particularly resistant to disruption. The resistance of the first movement to disruption might have been related to over familiarity with the very first movement of the sequence. The trial-and-error learning procedure used in teaching the sequences might have meant that subjects were especially familiar with the first movement in comparison with the subsequent movements. Moreover, the first movement to be performed at the beginning of every trial had always remained constant for each subject in *experiment 2.* In the cue-sequence paradigm (*experiment 3*), subjects were taught two different five-movement sequences, each associated with specific visual and auditory cues (Fig. 2) so that the first movement of each trial could be one of two possible movements. Once again no disruptive effect of TMS on the first movement was observed.

A second reason for the resistance of the first movement in a sequence to TMS disruption in *experiments 2* and *3* was also considered. The sequence onset was cued by a change in screen color and tone. These sensory cues might have functioned not only as a cue to retrieve the sequence but also

as a cue to specifically select the first movement of the sequence. Even in *experiment 3* it would have been possible for such associations between cues and individual movements to operate because the yellow screen and high tone were always associated with one first movement, whereas the pink screen and low tone were always associated with another first movement independently of the retrieval of each of the whole sequences. It is known, however, that medial premotor areas, including the pre-SMA, seem less essential when a specific movement is to be selected on the basis of an association with a sensory cue (Chen et al. 1995; Deiber et al. 1996, 1999; Hadland et al. 2001; Shima and Tanji 1998a; Thaler et al. 1995). A pharmacological inactivation study of the pre-SMA emphasized the importance of two factors, sensory-cued versus memory-guided sequence retrieval, in determining behavioral deficits (Shima and Tanji 1998a). Monkeys performed the same sequence for 11 trials. They were not impaired when they performed the sequence with the aid of visual cues to guide sequence selection (*trials 1–5*) but committed errors on 69% of the first memory-guided trials (*trial 6*). The error rate decreased on subsequent memory-guided trials (*trials 7–11*), suggesting an essential role of the pre-SMA in the initial retrieval or organization of the memory guided sequence.

The cue-change paradigm used in *experiment 4* was devised to cue subjects to retrieve whole sequences in the absence of a parallel simple sensorimotor association to a specific individual movement (Fig. 2). In the cue-change paradigm, the screen color instructed subjects to either perform the same sequence as on the previous trial or to switch to a different sequence. Neither screen color was associated with any particular, individual response; the first response could only be selected once subjects had retrieved the correct sequence of movements by reference to the sequence on the previous trial.

An RT analysis confirmed that the cue-change experiment was

performed in a very different manner to the cue-sequence task. In the cue-sequence task (*experiment 3,* Figs. 8 and 9), there was no RT cost of switching from one sequence to the other, suggesting that it was no more difficult to select the first movement of a sequence even if that sequence had not been performed for several trials. This might be expected if the subject did not need to retrieve the whole sequence before selecting the first movement but if instead the subject was able to select the first movement on the basis of its association with the initiation cue. In the cue-change task (*experiment 4,* Figs. 10 and 11), there was a significant cost of switching to a different sequence. In the cue-change experiment, it was more difficult to retrieve the first movement if that sequence had not been performed recently. This would be expected if the first movements were only selected after the sequence had been retrieved by reference to the memory of the sequence performed on the previous trial. Now when TMS was applied over the pre-SMA, the first movement of the sequence was consistently and significantly disrupted (Fig. 10*A*). The application of TMS over the PMd did not significantly disrupt performance (Fig. 10*B*).

In summary, the results suggest that the pre-SMA is critical for the initiation of a sequence chunk, whether that chunk occurs halfway through the sequence or even when it occurs at its very beginning. The only caveat is that for the deficit to be expressed, there must be no alternative route, such as a simple association between a sensory cue and an individual movement, by which the first movement in a chunk can be selected.

It should be noted, however, that in the cue-sequence paradigm in *experiment 3,* pre-SMA TMS was associated with a disruption of the *later* movements of the sequence. The association between the cue and the first movement might have preserved the first movement against the disruptive effect of pre-SMA TMS in *experiment 3,* but the delay of the later

movements suggested that TMS of the pre-SMA still affected the planning of the subsequent movements of the sequence. Thus in both *experiments 3* and *4,* pre-SMA TMS disrupted the total time to perform the sequences (Figs. 9*A* and 11*A*). TMS over PMd never disrupted the first movement RTs or the total sequence times in *experiments 3* and *4* (Figs. 8*B*, 9*B*, 10*B*, 11*B*).

The effect of the pre-SMA TMS on total sequence time attests to its disruptive effect on the selection of superordinate sets of movements rather than just individual movements. Gerloff et al. (1997) have previously reported that TMS in an adjacent medial frontal location disrupted future movements in a metronome paced sequence. Gerloff and colleagues emphasized the increase in errors on subsequent movements when TMS was applied over a slightly more posterior position than the one investigated in the present study. The RT effects and the absence of errors after pre-SMA TMS in the present study may be a consequence of the lower stimulation frequencies used. Another possibility, however, is that the high error rates reported by Gerloff et al. was a result of the TMS' greater proximity to the SMA region which might be more closely concerned with the execution of individual movements (Lee et al. 1999; Matsuzaka et al. 1992).

Specificity of TMS application over the pre-SMA

The design of the current set of experiments was intended to test the specificity of the pre-SMA, within the wider premotor region, for sequence organization. Although PMd TMS has been shown to affect movement selection in other situations (Johansen-Berg et al. 2002; Praamstra et al. 1999; Rushworth et al. 2002; Schluter et al. 1998, 1999), it did not affect the organization of movement sequences in the present investigation. Between-group analyses confirmed that the disruptive effects of TMS applied at the chunk point in *experiment 2* and at the initiation of a sequence in *experiment 4* were anatomically specific to the pre-SMA.

Applying TMS over the PMd region also controls for any disruptive effects of the tactile and auditory sensations that accompany the TMS pulses; the PMd results from *experiments 2* to *4* demonstrate that such sensations were not responsible for sequence disruption when TMS was applied over the pre-SMA.

Although the pre-SMA TMS was biased slightly away from the midline and toward the left hemisphere, it is still likely the pre-SMA region in both hemispheres was affected by the TMS. It is possible that the TMS over the midline had a larger disruptive effect than PMd TMS because it affected both hemispheres. Previous experiments have suggested that the effects of lateral hemisphere TMS are not just less pronounced versions of the effects of midline TMS; TMS over the midline in the pre-SMA or SMA region has been shown to produce distinct effects compared with stimulation over the more lateral hemisphere in the region of PMd or M1 (Gerloff et al. 1997; Rushworth et al. 2002). Moreover the left PMd was studied in the present experiments because previous experiments have suggested that the PMd in the left hemisphere has the dominant role and exerts a bilateral influence over both hands (Johansen-Berg et al. 2002; Schluter et al. 1998). An asymmetry in the strength of transcallosal inhibition in the motor system means that left hemisphere TMS has a greater effect on the cortex of the right hemisphere than vice versa (Netz et al. 1995). Despite these considerations, it remains possible that the administration of bilateral PMd TMS, or TMS over some other combination of cortical areas, might have a more disruptive effect on movement sequences. However, muscimol inactivation of the pre-SMA in just one hemisphere is sufficient to cause bilateral movement sequencing deficits (Nakamura et al. 1999), supporting the view that unilateral disruption of either the PMd or the pre-SMA can have bilateral movement interference effects.

Bimanual sequences were chosen in the current set of

experiments to minimize relational patterns (runs, repetitions, transpositions, etc.) that might influence subjects to organize a sequence in a specific way. It has recently been shown that medial frontal TMS can disrupt various aspects of bimanual coordination (Obhi et al. 2002; Serrien et al. 2002; Steyvers et al. 2003), suggesting that the disruptive effects of pre-SMA TMS in our study may be attributed to the use of bimanual sequences rather than the demands of organizing sequences. However, there are several lines of evidence that suggest the medial frontal region isn't limited to bimanual tasks but that this region may have a more abstract role in the organization and performance of complex actions (Picard and Strick 1996). The disruptive effects of medial frontal TMS in the aforementioned coordination studies has been in the form of deterioration in the timing between the hands and therefore may underlie a role of the medial frontal cortex in temporal aspects of actions. Indeed, it has previously been suggested that the medial frontal cortex is involved in the temporal organization of movements, even when they are unimanual in nature (Clower and Alexander 1998; Shima and Tanji 1998a). Second, TMS over the SMA has induced sequencing errors even on unimanual sequences (Gerloff et al. 1997), but this disruption was only evident when subjects performed highly complex sequences. Finally, it is not even necessary for subjects to make any movements for the pre-SMA BOLD signal to increase when encoding interval sequences (Schubotz and von Cramon 2001) or switching response set (Brass and von Cramon 2002). That it should be the organizational demands of a movement task rather than simpler movement selection or execution demands that determine pre-SMA recruitment is consistent with the area's closer connections with the prefrontal cortex than with the primary or spinal motor system (Bates and Goldman-Rakic 1993; Lu et al. 1994; Luppino et al. 1993).

The present series of studies did not address the role of the SMA in sequence organization. There are qualitative similarities in the activity patterns of SMA and pre-SMA neurons during

sequence performance (Nakamura et al. 1998; Shima et al. 1996; Shima and Tanji 2000), and it is possible that TMS directed over the SMA may have had similar effects. Quantitatively, however, more pre-SMA than SMA neurons are activated in the updating of movements and movement sequences (Matsuzaka and Tanji 1996; Rushworth et al. 2002; Shima et al. 1996). Because TMS over more posterior midline regions such as the SMA has distinct behavioral effects to pre-SMA TMS (Steyvers et al. 2003), it may be possible to investigate the contrasting roles of the SMA and pre-SMA in sequence organization in future experiments.

Conclusions

The pre-SMA may have a general role in initiating a new set of responses whether the set is a chunk from a sequence as in the present study or in some single cell recording studies (Nakamura et al. 1998; Shima et al. 1996) or a set of response mappings (Brass and von Cramon 2002; Rushworth et al. 2002). As the sequence becomes more automated, by repeated performance, pre-SMA neurons become less active (Nakamura et al. 1998; Sakai et al. 1998; Shima et al. 1996). Another medial frontal region, the cingulate cortex, may have a role in changing responses with changing reinforcement contingencies (Hadland et al. 2003; Rushworth et al. 2003; Shima and Tanji 1998b; Walton et al. 2002).

The pre-SMA does not have a general role in selecting or executing all movements, rather it seems to be concerned with the organization or selection of superordinate sets of movements. Pre-SMA TMS disrupts very few movements, and those that are disrupted are not necessarily those with longer RTs. If it is necessary to update the sequence during performance and initiate a new sequence chunk, then once again the pre-SMA is important. Such a function might be part of a more general role for the area in updating motor programs (Matsuzaka and Tanji 1996; Rushworth et al. 2002; Shima et al. 1996). A pre-SMA role in changing between sequence chunks

may underlie increases in BOLD signal with increasingly complex sequences (Boecker et al. 1998) or when subjects are unexpectedly required to change sequence (Jancke et al. 2000).