



Activation and connectivity patterns of the presupplementary and dorsal premotor areas during free improvisation of melodies and rhythms

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ABSTRACT

Free, i.e. non-externally cued generation of movement sequences is fundamental to human behavior. We have earlier hypothesized that the dorsal premotor cortex (PMD), which has been consistently implicated in cognitive aspects of planning and selection of spatial motor sequences may be particularly important for the free generation of spatial movement sequences, whereas the pre-supplementary motor area (pre-SMA), which shows increased activation during perception, learning and reproduction of temporal sequences, may contribute more to the generation of temporal structures. Here we test this hypothesis using fMRI and musical improvisation in professional pianists as a model behavior. We employed a 2×2 factorial design with the factors Melody (Specified/Improvised) and Rhythm (Specified/Improvised). The main effect analyses partly confirmed our hypothesis: there was a main effect of Melody in the PMD; the pre-SMA was present in the main effect of Rhythm, as predicted, as well as in the main effect of Melody. A psychophysiological interaction analysis of functional connectivity demonstrated that the correlation in activity between the pre-SMA and cerebellum was higher during rhythmic improvisation than during the other conditions. In summary, there were only subtle differences in activity level between the pre-SMA and PMD during improvisation, regardless of condition. Consequently, the free generation of rhythmic and melodic structures, appears to be largely integrated processes but the functional connectivity between premotor areas and other regions may change during free generation in response to sequence-specific spatiotemporal demands.

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Introduction

The ability to freely generate and organize movement sequences to reach higher order goals is a fundamental human capacity. Previous research have identified a number of frontal regions, including the pre-supplementary motor area (pre-SMA) (Beudel and de Jong, 2009; de Manzano and Ullén, 2012; Pesaran et al., 2008) and the dorsal premotor cortex (PMD) (Deiber et al., 1991; Lau et al., 2004) that play central roles in more cognitive aspects of movement sequencing and free generation per se.

While both the pre-SMA and the PMD are certainly implied in more than one aspect of sequential control, several studies have consistently found that the pre-SMA is involved in the perception (Bengtsson et al., 2009; Schubotz and von Cramon, 2001), production (Bengtsson et al., 2004, 2005; Karabanov et al., 2009; Penhune and Doyon, 2002; Schubotz and von Cramon, 2001) and learning (Ramnani and Passingham, 2001) of temporal sequential structures. Activity in the PMD, in contrast, has more often been linked to the perception (Schubotz and von Cramon, 2001), production (Bapi et

al., 2006; Bengtsson et al., 2004; Jenkins et al., 1994) and learning (Bischoff-Grethe et al., 2004; Jenkins et al., 1994) of spatial sequences. However, no previous studies have directly examined spatial and temporal control of sequences in free generation tasks using well-matched conditions and ecologically valid model behaviors in humans (see critique on Berkowitz and Ansari (2008) in the Discussion), and some studies on internally generated sequences suggest that there is not a clear dissociation between premotor regions involved in spatial and temporal control (Bortoletto and Cunnington, 2010; Chen et al., 2008; Kurata et al., 2000; Xiao et al., 2006). Additionally, as noted, both the pre-SMA and PMD are implied in a range of other processes that are difficult to separate out experimentally. Hence, previous investigations may suggest a broader and more complicated picture (Berkowitz and Ansari, 2008; Karabanov et al., 2009; Koch and Rothwell, 2009; Xiao et al., 2006). On one hand, the pre-SMA and the PMD, which are heavily interconnected, form part of an integrated network where information processing is to some extent distributed and regional differences in activity levels are fairly subtle; on the other hand, they also express a degree of functional specialization.

The specialization is likely to depend, at least in part, on differential connectivity to other brain regions. The pre-SMA is anatomically and functionally connected to several areas involved in temporal processing, such as the inferior frontal gyrus, basal ganglia and cerebellum

Abbreviations: LD, Levenshtein distance; PMD, dorsal premotor area; PPI, psychophysiological interactions; pre-SMA, presupplementary motor area.

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(Habas, 2010; Luppino et al., 1993; Zhang et al., 2012), whereas the PMD is more connected to parietal regions that are involved in spatial processing (Luppino et al., 2003; Tomassini et al., 2007). The pre-SMA and PMD might therefore each serve as an input port for certain information required in the organization of sequences. One way of separating their specific roles would thus be to investigate the effective functional connectivity between the premotor areas and other regions (as indicated above) during free generation of either temporal or spatial behavioral sequences. The hypothesis would consequently assume a dynamic functional network for internally driven sequence generation, which can extend to and draw upon different regions, depending on the sequence-specific spatiotemporal structure.

Here, we invited a group of professional pianists to perform musical improvisations during fMRI. We used a 2×2 design with the factors Melodic Structure (Notated or Improvised) and Rhythmic Structure (Notated or Improvised) (Fig. 1) to investigate main effect contrasts for Improvised Melody and Improvised Rhythm. The main effect contrasts were also used in an analysis of effective functional connectivity using psychophysiological interactions (PPI) with the pre-SMA and PMD as seed regions (Friston et al., 1997). A supplementary analysis of the direct contrast between free improvisation and sight reading was also performed in order to replicate previous analyses of differences in brain activity between internal generation of musical structures and externally cued musical performance (de Manzano and Ullén, 2012).

Materials and methods

Participants

Seventeen right-handed classical concert pianists with no history of neurological disease participated in the study. Imaging data from one participant, and one session from each of two participants were excluded because of a technical failure with the MR-scanner. All the participants had a piano education from the Royal College of Music in Stockholm or corresponding musical academy, and were regularly performing at the time of the scanning. Another participant and further five sessions from other participants were excluded due to inconsistent performance on the task (playing during rest or pausing more than 10 s during an active condition, see [Processing and analysis of behavioral data](#)). Hence, fifteen participants (mean = 40, SD = 12 years; one female) were included in the final analyses. The experimental procedures were undertaken with the understanding and written consent of each participant, conformed to The Code of Ethics of the World Medical Association (Declaration of Helsinki), and ethically approved by the Regional Ethical Review Board in Stockholm (Dnr 2007/83–/32). Participants were reimbursed with 600 SEK.

Materials

Piano keyboard and musical feedback

A custom made MR-compatible fiber optic piano keyboard (LUMItouch, Inc.) of one octave (12 keys with authentic dimensions, ranging from F to E) was used to collect behavioral data. The keyboard was connected to an optical–electrical converter outside the scanner room. The converter was in turn connected to a MIDI-keyboard (Midistart-2; miditech), generating a signal that was subsequently stored on a laptop using a standard recording and sequencer software (Cubase SE 3; Steinberg). The same software was also used together with a sound sampler (Kontakt 2/Steinway D convolution grand piano; Native instruments) and an external sound card (TerraTec Producer Phase 26 USB; TerraTec) to provide auditory feedback to the participants. Hence, the participants could hear what they were playing throughout the experiment.

Visual stimuli

Stimulus presentation was controlled by an E-prime (Psychological Software Tools, Inc.) script on a laptop computer. The visual stimuli, i.e. instruction slides for each condition, were back-projected on a screen placed just in front of the scanner and viewed by the participants through a periscope mirror attached to the birdcage head coil. The instruction slides had a line of text at the top giving the name of the condition (in Swedish), and below that, a musical score of four bars. For examples of musical scores see Fig. 1. All scores were constructed originally for the study by one of the authors (FU).

Visual templates for the four active conditions differed such that rhythm and melody were notated or left unspecified, according to the employed 2×2 factorial design (Fig. 1). For Notes both rhythm and melody were specified. For Melody the rhythm was specified using standard pitch-less percussion notation; the melody was thus left unspecified. For Rhythm the melody was specified using filled note heads; the rhythm was unspecified. For Free neither rhythm nor melody was specified; crosses were used to indicate the approximate number of notes to be played (8 crosses/bar or 32 in total, as illustrated in Fig. 1). For the three conditions constrained by external stimuli (Notes, Melody and Rhythm), there were eight notes in each bar. For the Rest condition, blank musical staves were shown (see Fig. 1). Since all active conditions were presented twice during each of the four sessions, a total of thirty-three unique templates (including one template for the Rest condition) were used. Throughout the preparatory period before each condition, the musical score was surrounded by a red rectangular frame. The removal of this frame signaled to the participant to either start playing or remain at rest, depending on the experimental task.



Fig. 1. Experimental design and conditions. Four active conditions were used which were arranged into a 2×2 factorial design according to the factors Melody and Rhythm: Notes – both melody and rhythm specified; Melody – melody unspecified, rhythm specified; Rhythm – melody specified, rhythm unspecified; Free – both melody and rhythm unspecified.

Auditory stimuli

Four beats of a metronome (clapping sound), corresponding to one bar of music (quadruple time, 60 beats per minute), were played during the preparatory period before all conditions, to pace subsequent performance.

Experimental procedure and design

Upon arrival, the participants were re-briefed about the purpose of the study and safety procedures. Then, they filled out a questionnaire regarding general health and history of disease relevant to the experiment and signed the informed consent form. Finally, detailed instructions were given about the experimental procedures, and the participants performed a brief training session. During training, the participants were seated at a desk with the piano keyboard and a laptop. Auditory feedback from the piano during the training session was provided through loudspeakers. The training procedure was identical to the procedure used during scanning, except that different musical templates were used, and that each condition was presented only two times (giving a total training time with the script of 3 min and 45 s). The participants were informed (i) that they were not constrained to play a certain musical style or genre (ii) that they should play according to their own inspiration and creativity (iii) while aiming at performing *roughly* the same amount of keystrokes during the free improvisations as in the other conditions and (iv) not make pauses more than a few seconds during the free improvisations. After the training session, the participants were asked if they had any difficulties with understanding or performing any of the experimental conditions. None of the participants reported any difficulties. Before scanning, the participants were told not to move during rest conditions; and to move only their right hand and forearm while keeping the head and shoulder still during playing. In total, the instruction period lasted about 15 min.

Participants were scanned in supine position with the piano keyboard resting on their lap. The right arm was supported by a pillow to avoid fatigue and minimize arm movements. Earplugs and head phones were used to reduce scanner noise and to allow auditory feedback from the piano (see [Materials](#)) and verbal communication with the experimenters supervising the scanning session. The perceived loudness of the auditory feedback was optimized for each individual. An adhesive tape was placed between the head coil and forehead to help the participants maintain their head in a fixed position.

The experimental paradigm was designed as a 2×2 factorial design ([Fig. 1](#)) with the two factors Melodic Structure (Specified or Improvised) and Rhythmic Structure (Specified or Improvised). There were thus four active conditions where rhythm and melody were either notated, or unspecified with need for improvisation: Notes (Specified Melodic Structure, Specified Rhythmic Structure), Melody (Improvised Melodic Structure, Specified Rhythmic Structure), Rhythm (Improvised Rhythmic Structure, Specified Melodic Structure), and Free (Improvised Rhythmic Structure, Improvised Melodic Structure). Main effect contrasts were used to reveal neural activity related to the improvisation of melodic and rhythmic material.

The experiment was carried out in four sessions. One session was composed of ten trials corresponding to two presentations of each condition (four experimental conditions and the rest condition). The trial order was randomized for each participant. Each trial lasted for 22.5 s, which means that a session was completed in 225 s and that the total scan time per participant was 900 s. The trials were composed of two parts: instruction period (5 s) and condition (17.5 s). The visual template was displayed throughout the duration of the trial. During the instruction period, four metronome clicks were presented (1 beat/s), with the first onset 1 s into the trial. After the instruction period the red frame surrounding the musical score was removed in order to cue the participants to perform the condition.

Processing and analysis of behavioral data

As described earlier, all behavioral data were recorded in MIDI format using a laptop. This raw data was first converted into text and parsed by a custom made script in MATLAB 7 (MathWorks, Inc.), to extract the onset time and identity of all keys played during scanning. An additional script in MATLAB was then used to calculate two types of measures from this data.

First, measures of the accuracy of the performance in the different conditions were computed. This was done by calculating the Levenshtein distance (LD) between a performed melody or rhythm and the corresponding target structure presented in the visual template. LD is a measure of the similarity between two sequences ([Bengtsson et al., 2007; Levenshtein, 1966](#)). It corresponds to the minimum number of single element deletions, insertions or substitutions required to transform one sequence into the other. For the two conditions with notated melodic structure (Notes, Rhythm) the *melodic LD* between the performed and notated sequences of pitches was computed. The melodic LD between the pitch sequences (C-D-D-E) and (C-D-E-E) would, e.g., be 1. For the conditions with notated rhythmic structure (Notes, Melody) a corresponding *rhythmic LD* was calculated. LD calculation requires that the sequences are composed from a finite set of discrete elements. Duration, however, is a continuous variable. Therefore, the performed durations had first to be converted into discrete note values. This was done by replacing each performed duration with the closest target duration in the template tune, i.e. the target duration for which the absolute error of the performed duration was smallest. For example, if the durations in the target tune were all from the set {500, 750, 1000}, and if the participant produced the duration sequence (490, 510, 770, 1084, 990), then this duration sequence would be transformed into the note value sequence (500, 500, 750, 1000, 1000) (all in ms).

The script would additionally notify if a participant had played during rest conditions or if the performance of a condition included a pause which exceeded 10 s. It was found that one participant had played during rest conditions and this participant was thus excluded from the final analysis. Another five sessions from other individuals were also excluded based on the same criteria.

Melodic and rhythmic LDs are presented for all conditions when relevant (e.g. not in Free, since it contains no target sequence), for descriptive purposes and in order to demonstrate the degree of accuracy of the performances. To investigate if the melodic accuracy differed between Notes and Rhythm, a repeated measures ANOVA was performed, using the participant median melodic LD as dependent variable. To test if the rhythmic accuracy differed between Notes and Melody, the corresponding test was performed using the median rhythmic LD.

Secondly, the motor output in the different conditions was characterized. The number of performed notes (key presses) was used as a measure of overall motor output. To determine if there were differences in motor output between conditions, 2×2 factorial ANOVAs were employed, as in the imaging analysis. The median number of notes was used as dependent variable. Rhythmic Structure and Melodic Structure were used as factors, each with two levels (Specified and Improvised).

In order to give a brief descriptive overview of what type of improvisations the participants had actually performed, a professional musician was assigned to identify modes/tonalities in the performances. This analysis is presented in the Supplementary data together with typical examples of performances in the three improvisation conditions ([Figure S1](#)).

MRI scanning parameters

Imaging was performed using a 1.5 T scanner (Signa Excite, GE Medical Systems, Milwaukee, WI, USA) with a standard eight-channel head coil. At the beginning of each scanning session, a high-resolution, three-

dimensional spoiled gradient echo T1-weighted anatomical image volume of the whole brain (voxel size $1 \times 1 \times 1 \text{ mm}^3$) was collected. Functional image data was then collected using a gradient-echo, echo-planar (EPI) T2*-weighted sequence with blood oxygenation level-dependent (BOLD) contrasts (Kwong et al., 1992; Ogawa et al., 1992), and the following parameters: repetition time (TR) = 2.5 s; echo time (TE) = 40 ms; field of view (FOV) = 22 cm; matrix size = 64×64 ; slice thickness = 5 mm; slice spacing = 0.5 mm; voxel size = $3.44 \times 3.44 \times 5 \text{ mm}^3$; flip angle = 90° . Whole brain image volumes were constructed from 32 contiguous axial slices which were acquired in ascending order. At the beginning of the session, four “dummy” image volumes were scanned, but not saved, to allow for equilibration effects. A total of 360 functional image volumes were acquired from each participant.

Image processing and analysis

The MRI data were processed and analyzed using the SPM8 software package (Wellcome Department of Imaging Neuroscience, London, UK).

Image preprocessing

All fMRI image volumes were realigned (to the first image of the first session), unwarped and coregistered to each individual's T1-weighted image (Andersson et al., 2001; Ashburner and Friston, 1997), and normalized using the template brain of the Montréal Neurological Institute (Friston et al., 1995).

Analysis of main effects

The fMRI data were modeled using a general linear model using the standard hemodynamic response function. The first level design matrix was set up using four conditions of interest, corresponding to the periods in each epoch during which the participants played the piano (i.e. the last 17.5 s of the 22.5 s epochs); one regressor representing the preparatory periods (first 5 s of each epoch). Rest was modeled as part of the implicit baseline. The design matrix weighted each preprocessed image according to its overall variability to reduce the impact of movement artifacts (Diedrichsen and Shadmehr, 2005).

Firstly, a region-of-interest (ROI) analysis was performed based on the main hypothesis of a particular role of the pre-SMA and PMD in rhythmic and melodic improvisation, respectively. It has been suggested that the PMD can be further divided into pre-PMD and PMD proper analogous to the medial premotor areas (Picard and Strick, 2001), but the borders of these regions are yet not certain (Hanakawa, 2011). Therefore, for the purpose of the present analysis, we treat the PMD as one integrated region. The collective ROI, which included both the pre-SMA and PMD in both hemispheres, was defined using the “Human Motor Area Template” after Mayka et al. (2006), who on the basis of a meta-analysis of 126 studies were able to model the spatial distribution of the human motor regions. The main effect for Improvised Melodic Structure was investigated with the contrast (Free + Melody)–(Rhythm + Notes). The main effect for Improvised Rhythmic Structure was investigated with the contrast (Free + Rhythm)–(Melody + Notes). Interaction effects were explored with the two contrasts (Free + Notes)–(Rhythm + Melody) and (Rhythm + Melody)–(Free + Notes). Analyses were first performed within each participant. After this estimation, the images of contrast estimates were spatially smoothed with an isotropic Gaussian filter of 8 mm full-width-at-half-maximum. A series of second-level random effects analysis (a one sample *t*-test for each contrast of interest) based on the contrast images from each participant, were then performed to allow inferences at group level. The significance of effects was assessed using *t*-statistics from included voxels to create statistical parametric maps. For the ROI analysis, cluster level thresholds with family-wise error (FWE) correction for multiple comparisons were implemented to control for false positives.

Connectivity analysis

A PPI describes how functional connectivity between brain regions may differ between experimental (psychological) contexts (Friston et al., 1997). Our hypothesis was that there would be a differential functional connectivity between premotor areas and other regions depending on the contextual constraints of sequence generation (melodic or rhythmic improvisation), and that the pre-SMA and PMD might show different connectivity patterns. Based on that pre-SMA was involved in the main effect of both Melody and Rhythm (see Results), we postulated a central role for the pre-SMA in coordinating and integrating sequence-specific spatiotemporal information. We therefore expected to see greater connectivity between the pre-SMA and regions involved in spatial processing (e.g. the PMD and posterior parietal cortex) during melodic versus rhythmic improvisation/sight-reading, and between the pre-SMA and regions involved in timing and temporal processing (e.g. the inferior frontal gyrus, basal ganglia and cerebellum) during rhythmic improvisation compared with melodic improvisation/sight-reading. To test this, we firstly extracted the deconvolved BOLD time series from the pre-SMA (defining the ROI as described above, according to the Human Motor Area Template), and used the two main effects from the previous factorial design as psychological variables. The product of the pre-SMA neuronal signal and each of the psychological variables represented the two PPIs of interest. All regressors were subsequently convolved with the canonical HRF and entered into two separate regression models according to spatial or temporal main effect. As previously, the design matrices weighted each preprocessed image according to its overall variability to reduce the impact of movement artifacts (Diedrichsen and Shadmehr, 2005). Secondly, two first level analyses were performed for each regression model, for each participant. The resulting images of contrast estimates were spatially smoothed with an isotropic Gaussian filter of 8 mm full-width-at-half-maximum. Finally, we performed a second-level random effects analyses. These analyses were repeated with the left PMD as a seed region for exploratory purposes. This region appeared in the main effect of Melody in the ROI analysis (see Results).

Free improvisation vs. sight reading

Supplementary analyses of the contrasts between free improvisation and sight reading (Free–Notes and Notes–Free) were also performed, using the same analysis parameters as in the main effects analysis, in order to replicate previous analyses on brain regions specifically involved in the internal generation of musical structures vs. externally cued musical performance (de Manzano and Ullén, 2012). The results of these comparisons are found in the Supplementary data.

Results

Behavioral data

To evaluate how accurately the participants performed the conditions, the produced melodic and rhythmic structures were compared to the notated targets. The LD between performed and notated structure was used as a measure of accuracy (see Materials and methods). The melodic LD was defined as the LD between the performed and the target pitch sequences, and corresponds to the number of wrong or omitted notes in a performance. To measure the rhythmic accuracy, a sequence of note values was first constructed for each performance, using the note values that provided the best approximation of each produced temporal interval (see Materials and methods). The rhythmic LD between the sequences of actual and target note values was then calculated. The means and standard deviations of the LDs in each relevant condition are displayed in Table 1.

A repeated measures ANOVA with melodic LD as dependent variable, showed that melodic LD was higher in Rhythm than in Notes ($F(1, 14) = 14.5, p = .002$). Rhythmic LD was higher in Melody than in Notes ($F(1, 14) = 4.87, p = .04$). There was thus a tendency for somewhat lower accuracy in the reproduction of a notated dimension

when the other dimension was improvised (Melody and Rhythm), than when both dimensions were notated (Notes). However, the number of melodic and rhythmic errors was low in absolute terms. The mean of the Rhythmic LD during Melody was somewhat higher than the Melodic LD during Rhythm (see Table 1). This could be interpreted as Melody being a more difficult task than Rhythm. However the reason for the difference was likely that for Melody, the rhythmic performance (duration sequence) had to be transformed into a note value sequence before the LD measure could be calculated. In line with this, it can be observed that the Rhythmic LD was also higher than Melodic LD during Notes. Therefore, we compared Melody and Rhythm using difference scores with Notes as baseline, i.e. Melodic LD during Rhythm–Melodic LD during Notes versus Rhythmic LD during Melody–Rhythmic LD during Notes, using a repeated measures ANOVA. No significant effect was found ($F(1, 14) = 0.01, p = .910$), confirming that when controlling for “baseline LD” there was no difference in performance between Melody and Rhythm.

Secondly, we investigated whether the performances in the different conditions were equal in terms of overall motor output. There was no difference in total number of keystrokes between conditions. The means and standard deviations of the number of keystrokes in each condition are shown in Table 1. A 2×2 factorial ANOVA with number of notes as dependent variable, and Rhythmic Structure and Melodic Structure as factors, each with two levels (Notated and Improvised), showed no main effect of Rhythmic Structure ($F(1, 14) = .013; p = .91$), no main effect of Melodic Structure ($F(1, 14) = 1.18; p = .29$) and no interaction ($F(1, 14) = .68; p = .42$).

Functional MRI data

Analysis of main effects

The ROI based analysis showed a significant main effect of melodic improvisation in the left PMD and the left pre-SMA. There was also a significant main effect of rhythmic improvisation in the left pre-SMA. The results were adjusted for multiple comparisons using cluster level FWE-correction. The results are summarized in Table 2. Fig. 2 illustrates these results and additionally displays the percent signal change for each active condition in relation to the implicit baseline in the left pre-SMA and left PMD. No interaction effects were found. The direct contrasts between Melody and Rhythm (Melody–Rhythm; Rhythm–Melody) showed no suprathreshold clusters.

Connectivity analysis

The whole-brain PPI-analysis revealed that there was a greater correlation between activity changes in the pre-SMA (the seed region) and a cluster of voxels in the cerebellum ($k_E = 466; p = 0.002$, cluster level FWE-corrected) during conditions of rhythmic improvisation than during melodic improvisation or sight-reading (see Fig. 3). The peak activity was found in the left lobule VIII but extended across the vermis and midline to the right lobule VIII and further into lobule VI. The PPI approach involves creating a regressor which correlates with activity in the seed region during certain experimental

conditions, but is negatively correlated during other conditions. Hence, we confirmed that the results were due to an enhanced correlation between pre-SMA and cerebellar activity during rhythmic improvisation and not because of an increased negative correlation during melodic improvisation. The graph in Fig. 3 illustrates an example of the different slopes of the correlations between the pre-SMA and cerebellum during Melody and Rhythm in one participant. No PPIs were found for the pre-SMA in relation to melodic improvisation, or when using the left PMD as a seed region.

Free improvisation vs. sight reading

In order to replicate our previous findings and add to the more general discussion in the literature of which brain regions are more specifically related to internally generated musical improvisation as opposed to externally cued musical production, we investigated the contrasts Free–Notes and Notes–Free. For Free–Notes, we found two clusters of voxels that displayed higher activity during Free than during Notes. One cluster of activity included the pre-SMA and left PMD. The second cluster was largely located around the left dorsolateral prefrontal cortex but also extended slightly into the left inferior frontal cortex (pars triangularis). For more detailed results see Supplementary data Table 3 and Figure S2 (clusters in red color). For the contrast Notes–Free we found six clusters of voxels that were significantly more active during sight reading than during free improvisation. All results were corrected for multiple comparisons using cluster level family-wise error. The clusters were found in the bilateral inferior occipital gyrus, right precentral gyrus (extending across the midline and dorsally into the right superior parietal cortex), bilateral medial frontal gyrus, left superior parietal lobe and right inferior parietal lobe. For more detailed results see Supplementary data Table 3 and Figure S2 (clusters in blue color).

Discussion

In this fMRI study, we let professional piano players perform four conditions of musical improvisation on a one octave piano keyboard, varying the freedom of either rhythm or melody, to investigate the regional distribution of spatial and temporal processing during creative internal generation of musical structures. A key novel finding is that functional connectivity between premotor regions and other regions may change during free generation in response to spatiotemporal demands (see *Overlapping neural correlates of melodic and rhythmic improvisation*). We also conclude that, although we see subtle rhythmic/melodic modulations of activity in the pre-SMA and PMD, there is a striking overlap in temporal and spatial processing during musical improvisation at this level of movement sequence generation (see *Free generation vs. sight reading*).

As shown by the melodic and rhythmic LD measures, the participants reproduced the notated templates accurately in all conditions. There was a tendency for a somewhat lower accuracy in the reproduction of a notated dimension when the other dimension was improvised (Melody and Rhythm), than when both dimensions were notated (Notes) but the number of errors in absolute terms was low. There was no difference in LD between Melody and Rhythm

Table 1

Means and standard deviations of LDs and number of keystrokes for relevant experimental conditions.

| Condition | /Measure | Mean | SD |
|-----------|--------------|-------|------|
| Notes | /Melodic LD | 0.88 | 0.95 |
| Notes | /Rhythmic LD | 4.11 | 1.95 |
| Rhythm | /Melodic LD | 2.07 | 1.57 |
| Melody | /Rhythmic LD | 5.38 | 1.84 |
| Notes | /NrKeys | 32.12 | 0.29 |
| Rhythm | /NrKeys | 31.68 | 0.96 |
| Melody | /NrKeys | 32.27 | 0.57 |
| Free | /NrKeys | 32.85 | 4.78 |

LD = Levenshtein distance; NrKeys = number of keystrokes.

Table 2

The main effects of rhythmic and melodic improvisation in a ROI analysis based on the bilateral pre-SMA and PMD.

| Main effect of Melody | | | | | | | Main effect of Rhythm | | | | |
|-----------------------|------|-------|------|-----|----|----|-----------------------|-------------------|----|----|----|
| Brain region | Side | k_E | T | x | y | z | k_E | T | x | y | z |
| pre-SMA | L | 98* | 5.31 | −4 | 10 | 63 | 143* | 5.78 ⁺ | −2 | 18 | 61 |
| pre-SMA | R/L | | | | | | 100* | 5.55 ⁺ | 0 | 24 | 47 |
| PMD | L | 72* | 5.14 | −30 | −4 | 65 | | | | | |

* Significant at $p < .05$, cluster level FWE-corrected; ⁺ Significant at $p < .05$, voxel level FWE-corrected. PMD = dorsal premotor region, pre-SMA = pre-supplementary motor area. L = left hemisphere; R = right hemisphere. x, y, and z, MNI coordinates.

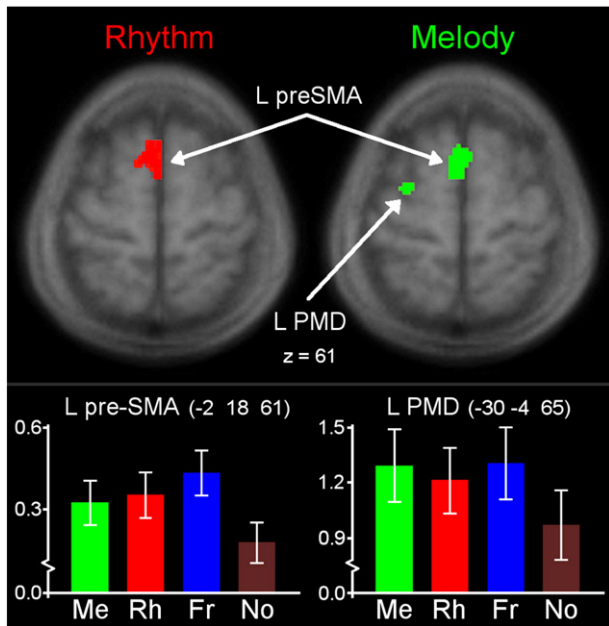


Fig. 2. Results from the main effects analysis (Melody and Rhythm), and percent signal change from baseline of active conditions in peak voxels. The bars illustrate the hemodynamic response (% signal change) for each condition relative the implicit baseline in one local peak voxel: Left pre-SMA, in coordinates $x = -2, y = 18, z = 61$; Left PMD, in coordinates $x = -30, y = -4, z = 65$. Error bars represent the spread of the data ± 1 standard error. The top panel displays significant clusters superimposed on the normalized group T1w image.

when controlling for baseline LD during Notes. The behavioral analyses thus support that differences in brain activity between conditions indeed reflect differences in processing between improvisation and reproduction of melodic and rhythmic structures.

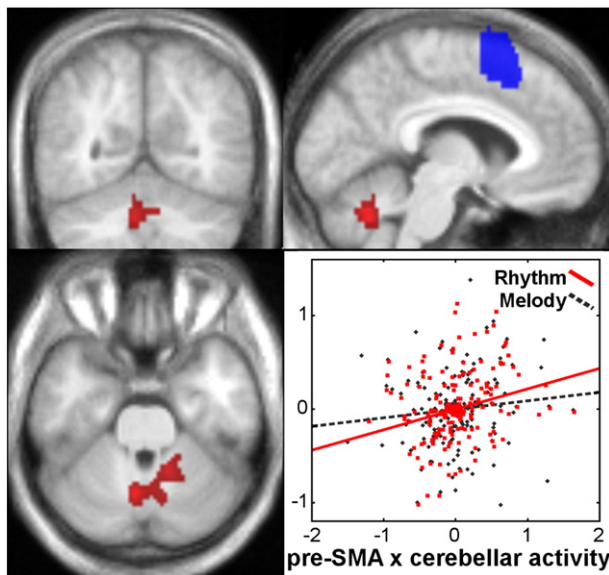


Fig. 3. Results from the PPI-analysis illustrating a cluster of voxels in the cerebellum (red) which activity correlates with pre-SMA activity (blue) during Rhythm. The cluster was significant at $p = 0.002$, cluster level FWE-corrected. The graph illustrates the different slopes of the correlations between pre-SMA and cerebellar activity during Melody (dotted black line) and Rhythm (red continuous line) in one participant. The markers represent raw data.

Differential roles of the pre-SMA and PMD for melodic and rhythmic improvisation

The ROI analysis partly confirmed our main hypothesis. The PMD was present in the main effect of melodic improvisation, but not in the main effect of rhythmic improvisation; activity in the pre-SMA was, as predicted, related to rhythmic improvisation but also increased its activity for melodic improvisation. However, both regions were to some extent active during all conditions, particularly for the improvisation conditions as illustrated by the contrast between free improvisation and sight reading. The direct contrasts between Rhythm and Melody did not replicate what was found in the main effects analysis. There was no interaction between Melody and Rhythm.

Many studies implicate the pre-SMA in the processing of sequential temporal structures in different contexts, e.g. rhythm learning (Ramnani and Passingham, 2001; Steele and Penhune, 2010); reproduction of auditorily (Chen et al., 2005) or visually (Schubotz and von Cramon, 2001) presented rhythms; performance of overlearned rhythms that were trained in auditory (Bengtsson et al., 2004; Karabanov et al., 2009) or visual (Karabanov et al., 2009) modality; as well as passive rhythm perception (Bengtsson et al., 2009). Mita et al. (2009) was in addition able to demonstrate, based on neural recordings of pre-SMA neurons in monkeys, that these neurons contribute to both inference of temporal constraints from visual instructions and timing of motor initiation as well as representation of time per se, during self-generated movements. The same group of researchers was later able to create a computational algorithm which could decode temporal information from individual neurons in the pre-SMA, to estimate the elapsed time during a response task with variable delays with a precision of approximately 1 s (Shinomoto et al., 2011). Thus, while a distributed set of brain regions may have a role in motor timing, these studies nonetheless provide a convincing demonstration of the importance of medial premotor areas.

Other studies suggest that the pre-SMA plays important roles for sequence control in general, in particular for the hierarchical control of action sequences (Kennerley et al., 2004). Interestingly, the functional roles of the pre-SMA in sequential timing and hierarchical control may be related, since spontaneously emerging temporal patterns in complex movement sequences reflect their internal organization into chunks (Rosenbaum et al., 1983; Sakai et al., 2003). Even though the main effect of Rhythm was slightly greater than that of Melody, the present findings indicate a broader role of the pre-SMA in free generation. In a report from Mansfield et al. (2011), it was suggested that the pre-SMA may bias the striatum towards lower response thresholds when behavior is less constrained. One could speculate on this being an important feature in relation to free generation and creative performance in general, when it comes to regulating fluency and filtering of appropriate responses.

The PMD is heavily connected with parietal regions, and is implied in visuomotor integration and spatial targeting of movements in general (Wise et al., 1997). PMD activity has been related to spatial sequence processing in various paradigms, including learning (Bischoff-Grethe et al., 2004; Jenkins et al., 1994), performance (Bapi et al., 2006; Bengtsson et al., 2004; Jenkins et al., 1994) and perception (Schubotz and von Cramon, 2001). Activity in the rostral section of the PMD is presumably more related to cognitive aspects of movement control (Picard and Strick, 2001). Ohbayashi et al. (2003) e.g., found that neurons in this region are involved in transforming positional cues in working memory into a sequential motor program. Directly in line with the present findings is the report from Beudel and de Jong (2009), where the PMD was found to be involved in free selection of both target based and self-referenced finger movements in a spatial key pressing task.

As reviewed, there is ample evidence which supports that action and perception are integrated processes that to a large extent rely

on the same neural circuitry (see e.g. Hommel et al., 2001; Prinz, 1997; Rizzolatti and Craighero, 2004). In addition to more cognitive aspects of sequence generation, premotor areas have thus also been shown to be activated in a number of perceptual paradigms, e.g. discrimination, judgment and passive perception of sequences (see Introduction), even though activity levels are generally higher for internal generation of sequences. In other words, another aspect of the current findings is that free generation may utilize neural circuitry that is also used for perception, learning and production of the same type of structures. This might be an important observation in relation to neuropsychological research on creativity in general, and may to some extent account for why results across experiments in this field have been fairly inconclusive (Dietrich and Kanso, 2010); although some regions may play generic roles for free response generation (de Manzano and Ullén, 2012) other regions involved in creative performance may be highly task specific.

Free generation vs. sight reading

Continuing on the previous topic, we address the more general question of which brain regions are involved in musical creativity. We, and others, have already explored brain activity which is related to musical improvisation as compared to e.g. sight-reading (de Manzano and Ullén, 2012), pseudo-random sequence generation (de Manzano and Ullén, 2012), reproductions of a previous improvisations (Bengtsson et al., 2007) or overlearned sequences (Berkowitz and Ansari, 2008; Limb and Braun, 2008). In these studies, a number of regions (e.g. anterior cingulate and premotor cortices) are found to be particularly involved in the *creative* internal generation of musical material.

There are however also diverging results in these studies with regard to brain areas such as the dorsolateral prefrontal cortex, which is found either more or even less active during improvisation. These differences likely stem from methodological sources such as choice of control tasks or demography and expertise of the participant sample. A more detailed comparative review of these previous studies can be found in de Manzano (2010). In light of these discrepancies, it was of interest to show supplementary results from the present study on the direct contrast between free improvisation and sight reading (see Supplementary data). The present results replicate our previous findings (de Manzano and Ullén, 2012), by emphasizing the importance of the pre-SMA, PMD and dorsolateral prefrontal cortex in creativity and musical improvisation. Thus, this is the third study (incl. Bengtsson et al., 2007; de Manzano and Ullén, 2012) in which improvisation is not accompanied by a deactivation of the dorsolateral prefrontal cortex, as reported by Limb and Braun (2008) during improvisation. In Limb and Braun (2008), improvisation was compared to execution of over-learned musical sequences at two levels of complexity. The participants – six professional jazz pianists – were asked to play either a C major scale, improvise in C major, play a Jazz composition from memory to auditory musical accompaniment, or improvise to this accompaniment.

The apparent discrepancy in results could possibly be accounted for by a difference in expertise/improvisational skills between the two experimental groups (de Manzano, 2010). Improvisation is a much more central feature of jazz than of classical music, and jazz pianists are arguably more accustomed to performing spontaneous improvisations than are classical pianists. Furthermore, it could be argued that the two experimental paradigms differ in complexity. Improvisation on a well-learned scale or chord structure, as in Limb and Braun, is conceivably a less cognitively demanding task than completely free improvisation. In line with this reasoning, it can be observed that our classical pianists activate a network including the pre-SMA, PMD and DLPFC, typically associated with explicit processing of novel motor sequences, while jazz pianists rely on regions for implicit routine and automated behavior, showing a more caudal distribution of activity in the SMA and PMD, in conjunction with activity in limbic regions and the basal ganglia (Doyon and Benali, 2005). Notably, all previous imaging studies on

piano improvisation (Bengtsson et al., 2007; Berkowitz and Ansari, 2008; de Manzano and Ullén, 2012; Limb and Braun, 2008) as well as the present investigation, find that the PMD is involved in musical creativity.

Overlapping neural correlates of melodic and rhythmic improvisation

Although we found some evidence that the pre-SMA and the PMD may have differential importance for rhythmic and melodic control, it should be emphasized that a striking aspect of the present findings is the large degree of overlap in activity between the different improvisation conditions. Both the pre-SMA and the PMD increased their activity in all improvisation conditions, albeit to a different degree. This general observation is in line with the findings of Berkowitz and Ansari (2008), who also investigated piano improvisations of melodies and rhythms using fMRI. In that study however, the ability to discern regional differences might have been limited by a number of factors: Firstly, the control condition where rhythm and melody were determined (corresponding to our Notes), involved playing a sequence of pre-learned 5-note patterns, which in effect gave rich possibilities for free choice and musical creation (retrieving, selecting and combining out of seven different 5-note melodies to form a 16 pattern long sequence). We believe this is the main reason why the pre-SMA, which is generally found active in relation to free choice and internally generated behaviors (see reviews in e.g. de Manzano and Ullén, 2012; Haggard, 2008), is not present in their results. Secondly, the metronome only sounded during the conditions where rhythm was constrained, and not during rhythm improvisation. This means that the main effect of rhythmic improvisation was to some extent confounded by the difference in auditory stimulation. Thirdly, the instruction to improvise the melody was post-hoc found to have a significant effect on both generation of melody (variety of note combinations) and generation of rhythm (inter-press interval variability), which might have confounded results even further.

Nonetheless, the shared observation of an overlap in neural correlates underscores that the processes involved in the generation of rhythmic and melodic structures are highly integrated. Indeed, if a particular, e.g. musical goal should be fulfilled, these aspects of a tune can obviously not be generated independently: the emotional character of a tune is determined by a complex interplay between these, and other, musical parameters (Gabrielsson and Lindström, 2001). The high degree of melody–rhythm integration in higher order musical processes such as improvisation fits a general, modular view of music processing in the brain, where temporal and spatial/melodic processing are separated at lower levels of perception and production but integrated in superordinate brain regions (Peretz and Coltheart, 2003).

Effective functional connectivity that varies with spatiotemporal processing demands

Using the PPI-approach we were able to demonstrate an increase in effective functional connectivity between the pre-SMA and cerebellum during free generation of rhythm which was not present to the same extent during improvisation of melody or externally cued production of either rhythmic or melodic sequences. This result could be interpreted either as a condition-sensitive change in the effective connectivity between two areas, or alternatively, that the pre-SMA modulates the responsiveness of the cerebellum to rhythmic improvisation (Friston et al., 1997). We propose that the premotor network may show different patterns of interaction with other regions depending on the functionality required in organizing and generating a particular movement sequence. The cerebellum and the pre-SMA are connected via cerebello-thalamo-cortical loops and the basal ganglia (Akkal et al., 2007). In humans, resting state activity time-courses in the pre-SMA and cerebellum have also been found to correlate (Habas, 2010). As outlined in the introduction, the cerebellum was one of the brain areas

where we a priori expected an association with rhythmic improvisation and therefore the present results are in line with our hypotheses. A large literature demonstrates the importance of the cerebellum in temporal processing, which includes neuroimaging studies on perceptual and motor timing (Ivry, 1993; Penhune et al., 1998) as well as clinical research on patients who have suffered neurological deficits in timing functions following cerebellar damage (Ivry and Keele, 1989). We have previously reported on cerebellar activity, notably in the ipsilateral lobuli VI and VIII, i.e. similar areas as in the present study, as being associated with self-paced production of well-learned rhythms (Karabanov et al., 2009). The findings are also directly in line with Aso et al. (2010) who were able to show functional connectivity between the medial premotor regions (the ROI included both pre-SMA and SMA proper) and the cerebellar lobuli VI and VIII during sensory and motor timing. Again, it would appear as if structures controlling the internal generation of movement sequences are able to draw on similar functional resources as are utilized during perception and production. Notably, we here control for rhythmic sight-reading, which means that the observed PPI is specific to the internal generation of rhythm. The above referenced literature would suggest that this additional contribution involves extended support in constructing and representing temporal intervals.

It should be mentioned that at least two studies have found more activity in cerebellar regions during the performance of spatial sequences than during performance of rhythmic sequences (Bengtsson et al., 2004; Berkowitz and Ansari, 2008). The cerebellum is known to be involved in e.g. the accuracy and coordination of movements in addition to timing (reviewed in Grimaldi and Manto, 2011), which means that it would not be improbable for different, or perhaps even similar regions of the cerebellum to be involved in both Rhythm and Melody. It is therefore conceivable that if placing more extreme demands on spatial processing, another PPI analysis would have found a modulation of the correlation between e.g. the PMD and lateral cerebellar hand regions. Similarly, we cannot rule out that more extreme forms of improvisation, or for that matter an increased sample size, might have revealed additional patterns of functional connectivity between the premotor regions and other areas.

Conclusion

In summary, free generation of either spatial or temporal sequences is associated with only subtle modulations in the level of activity of the pre-SMA and PMD and overall, creative musical improvisation of melody and rhythm appears to be a largely integrated processes. Interestingly however, functional connectivity between premotor regions and other regions varies during free generation in response to task-specific spatiotemporal demands.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.neuroimage.2012.06.024>.

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