Functional harmonics reveal multi-dimensional basis functions underlying cortical organization

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ABSTRACT

The human brain consists of functionally specialized areas, which flexibly interact and integrate forming a multitude of complex functional networks. The principles underlying this functional differentiation and integration remain unknown. Here, we demonstrate that a fundamental principle ubiquitous in nature - harmonic modes - explains the orchestration of brain's functional organization. Applied to the functional connectivity in resting state averaged across 812 participants, harmonic modes give rise to *functional harmonics* revealing the communication channels of the human brain. Each associated with a different spatial frequency, the functional harmonics provide the frequency-ordered building blocks, which can reconstruct any pattern of brain activity. We show that 47 brain activation patterns elicited by 7 different task categories in the Human Connectome Project task battery can be reconstructed from a very small subset of functional harmonics, uncovering a parsimonious description of the previously unknown relationship between task and resting state brain activity. Our findings evidence that the functional specialization of the human cortex occurs in a gradiental manner across multiple dimensions in the functional harmonic basis, where isolines of gradients follow the borders of functional areas as defined in a state-of-the-art parcellation of the human cortex. Hence, the multi-dimensional functional harmonic representation unifies two competing views of the brain's functional organization, i.e. modular vs gradiental perspective.

Introduction

The human brain is topographically organized into functionally specific brain areas[1]. Integration of these areas in various different constellations allows for the immense complexity of human brain function[2]. Despite remarkable progress in mapping the brain into functionally meaningful subdivisions, known as cortical areas[3,4], and in identifying functionally relevant combinations of these areas forming the functional networks of the brain[5], the principles governing this functional segregation and integration in the human brain have remained unknown. Here we demonstrate that a fundamental principle ubiquitous in nature, i.e. the harmonic modes, when applied to functional connectivity data in humans, reveals both, the brain's functional networks as well as its topographic organization.

The topographic organization of the brain into functionally specific areas is one of its fundamental properties, observed in evolution as early as the last common ancestor of vertebrates[4,6]. The individuality of each brain area is determined by its functional specification, its microstructure (cyto- and myeloarchitecture)[4], and its inter- and intra-area connectivity[3]. Significant effort in neuroscience has been directed towards subdividing the brain into adjoining parcels, which are assumed to have uniform functional specification and homogeneous connectivity[3,4]. A multitude of functionally distinct brain areas coordinate through synchronous fluctuations in their activity[7]. Coherent oscillations among distinct brain areas have been shown to be another evolutionarily conserved aspect of brain activity[8]. The overlap of the networks formed through these spontaneous system oscillations, termed the functional connectivity patterns, with the functional networks of the human brain identified by various sensory, motor, and cognitive task paradigms[9–12], strongly indicates their relevance for the brain's functionality.

However, this modular view of brain organization, where separate, adjoining brain areas with uniform functionality and

homogeneous structural connectivity integrate into functional networks through coherent oscillations, has been challenged by the presence of gradually varying boundaries between brain areas suggesting a degree of transition instead of sharply separated brain areas[13], as well as by the existence of topographic mappings, which characterize the differences within a functionally specific brain area[14–16]. Topographic mappings including retinotopy[14], somatotopy[15], tonotopy[16], show that representation of our visual field, body and auditory frequency spectrum are spatially continuously represented across the areas of the primary visual, somatomotor and auditory cortices, respectively, challenging the assumption of uniform functionality within the determined brain areas and demonstrating a smoothly varying functionality[13]. As an alternative, theoretical work[17,18] and recent experimental findings[13] suggested a "gradiental perspective", where the functional organization of the cortex is argued to be continuous, interactive and emergent as opposed to mosaic, modular and prededicated[17]. Similar to the smoothly varying functionality of primary sensory and motor areas, association cortices functioning as integration centres for more complex or elaborated mental processes, are hypothesized to emerge from the convergence of information across sensory modalities[18] with increasing spatial distance on the cortex from the highly functionally specialized primary cortices[19]. Supporting this hypothesis, a principal connectivity gradient of cortical organization in the human connectome has been identified, where the functional networks of the human brain are located according to a functional spectrum from perception and action to more abstract cognitive functions[13]. Although converging evidence[13,20,21] supports the continuous and emergent view of cortical organization, the principles underlying the functional organization in the brain remain largely unknown.

Here, we demonstrate that the functional segregation and integration in the brain are governed by the same natural principle of harmonic modes that underlies a multitude of physical and biological phenomena including the emergence of harmonic waves (modes) encountered in acoustics[22], optics[23], electron orbits[24,25], electro-magnetism[26,27] and morphogenesis[28,29]. By solving the time-independent (standing) wave equation[30,31] on the communication structure of the human brain given by functional magnetic brain imaging (fMRI) connectivity, we uncover the shape of the harmonic modes emerging from synchronous oscillations in large scale brain activity. These harmonic modes decompose the functional connectivity into a hierarchical set of frequency-specific communication channels, which naturally emerge from coherent, spontaneous brain activity, and unveil both, the principal connectivity gradient[13], as well as cortical parcellations[3]. Our results indicate that the functional segregation and integration in the brain are governed by a multidimensional harmonic representation that we call "functional harmonics". Finally, the decomposition of the brain activity maps elicited by various cognitive tasks into the set of functional harmonics reveals that each task primarily involves activation of a very small subset of functional harmonics, suggesting that the functional harmonics reveal fundamental building blocks of not only resting state activity, but also various cognitive functions.

Estimation of functional harmonics

Mathematically, the patterns of harmonic modes of a dynamical system are estimated by the eigendecomposition of the Laplace operator, which lies at the heart of theories of heat, light, sound, electricity, magnetism, gravitation and fluid mechanics[32]. In vibrating systems, eigenfunctions of the Laplacian constitute standing waves, which also have been proposed as the mechanism underlying cortical communication observed in electroencephalogram (EEG) data[33]. Theoretical studies as well as experimental findings have shown that spherical harmonics, i.e. Laplace eigenfunctions on a sphere, underlie cortical activation patterns in fMRI[34]. Harmonic modes of the structural connectivity of the human brain, i.e. Laplace eigenfunctions on the human connectome, have been found to predict the collective dynamics of cortical activity at the macroscopic scale, and reveal resting state networks[31].

In this work, we hypothesized that the harmonic modes of the brain's communication structure given by its *functional* connectivity underlie its functional integration and segregation. There are several crucial properties of harmonic modes that lead us to form our hypothesis:

1) The dense functional connectivity (dense FC) matrix, in our study estimated from the pairwise temporal correlations between all pairs of vertices on the cortical surface (59.412 vertices in total), encodes the communication structure of the human brain. In order to find a multidimensional representation that best preserves this functional communication structure, we utilized the discrete counterpart of the harmonic modes defined on a graph, i.e. the eigenvectors of the graph Laplacian, which have been shown to optimally preserve the local graph structure while embedding it into a lower-dimensional space[35]. Hence, the functional harmonics estimated by the harmonic modes of the dense FC in this work, reveal the optimal multidimensional mapping between the communication structure of the brain given by the dense FC and the cortical surface in the sense that the strongest functional relationships given by the largest correlation values are optimally preserved.

2) Functional harmonics are the smoothest patterns that respect the constraints posed by the functional relationships given by the FC[35]. This implies that the average difference between neighbouring nodes in a graph representation is minimized. Intriguingly, theoretical work has shown that activation patterns on graphs in which neighbouring nodes co-activate lead to patterns with minimum free energy or entropy[36,37], and that the transition between such patterns requires minimal energy[38].

3) Due to their orthogonality, Laplace eigenfunctions provide a new function basis. When applied to a one-dimensional domain with cyclic boundary conditions, i.e. to a circle, Laplace eigenfunctions constitute the well-known Fourier basis,

whereas on a sphere, they yield the spherical harmonics. Each eigenfunction corresponds to a unique eigenvalue related to its spatial frequency, and the set of all eigenfunctions forms a function basis, in which any signal can be represented in the frequency domain. Considering this particular aspect of harmonic patterns, the functional harmonics provide a new frequency-specific function basis driven by the brain's communication structure (dense FC), where each dimension provides a frequency-specific communication channel on the cortex.

4) The eigenfunctions of the Laplacian explain self-organizing patterns in many dynamical systems[24–26,28,39], ranging from relatively simple physical phenomena like vibrating strings and metal plates[22] to complex biological processes such as pattern formation and morphogenesis[28,29].

Considering that functional harmonics provide an optimal, frequency-specific mapping of the brain's communication structure to the cortex; that they represent the most energy-efficient activation patterns, which respect the constraints posed by this communication structure; and given the ubiquity of harmonics in nature, we hypothesized that functional harmonics provide the ideal candidate to explain functional segregation and integration in the brain. In order to test this hypothesis, we used the dense FC computed from resting state fMRI (rfMRI) data averaged across 812 subjects, provided by the Human Connectome Project (HCP), 900 subjects data release[40–47]. We obtained the functional harmonics by estimating the eigenvectors of the graph Laplacian computed on the graph representation of the FC (Figure 1).

Functional harmonics reveal functionally relevant communication channels

We first investigated whether functional harmonics yield functionally meaningful communication channels, i.e. patterns of correlated activity. Figure 2 shows the first 11 non-constant functional harmonics (referred to as ψ_1-ψ_{11}), ordered starting from the lowest spatial frequency, illustrating that each harmonic is a smoothly varying pattern on the cortex between a positive and a negative polarity; i.e., a gradient. Functional harmonics 1 and 2 correspond to previously identified large-scale gradients[13] that delineate the separation between the major sensory and the uni- vs. multimodal cortices in the brain, respectively (see SI Figure 1a). Figure 2a and b demonstrate the overlap between the visual and sensorimotor networks as defined in Yeo et al. (2011)[48] and the gradiental patterns of the first and second functional harmonics. We observed that functional harmonic 3 reveals a finer subdivision of the somatosensory/motor system[49–51]. The overlay of the borders of the five somatotopic areas defined by the HCP[3,52] on the third functional harmonic are shown in Figure 2c. Similarly, in functional harmonic 4, we found a finer segregation of the visual system, following a retinotopic eccentricity gradient (for further details on retinotopic mapping see the following section)[53]. The overlay of the borders of early visual areas (V1-V4) on functional harmonic 4 are shown in Figure 2d.

The regions found in the positive polarity of functional harmonic 5 (borders shown on the left 3 panels in Figure 2e) closely resemble the sensory-motor pathway[48] (Figure 2e), which are known to be modulated by visuospatial attention[54]. In the negative polarity, we found the auditory cortex and parts of the somatosensory/motor network (Figure 2e). In contrast, in functional harmonic 6, auditory and visual areas were both localized in the positive polarity, forming a network related to audiovisual object (including faces) recognition[55–57], i.e. recognition of the "outer world". The negative polarity of harmonic 6 segregates the somatotopic face area as well as parts of the default mode network (DMN), a network of regions whose activity has been related to self-referential tasks[58]. Thus, the negative polarity of functional harmonic 6 forms a self-referential processing stream[58–60]. Functional harmonic 7 provides a further somatotopic gradient, including a higher hand area, 24dd, in the medial cortex[49] (see Figure 2g and annotations in Figure 2c). Functional harmonics 8 to 10 correspond to different subdivisions of higher order networks such as the frontoparietal network and DMN (see SI Figure 2). In particular, the DMN[61] is delineated in the positive polarity of functional harmonic 9 (borders of the DMN as defined by Yeo et al. (2011)[48] are overlaid on functional harmonic 9 in Figure 2i). Functional harmonic 11, the first asymmetric harmonic between the two hemispheres, yields the separation between the right and left somatotopic hand areas[62]. Overall, these results demonstrate that functional harmonics provide a multitude of functionally relevant communication channels, each associated with a unique spatial frequency, and enable a set of parallel processing streams in the human brain.

Functional harmonics reveal brain areas and topographic mappings

The fact that functional harmonics display both, well-delineated specialized regions (as for example in functional harmonics 3, 7, and 11) as well as gradients that integrate brain regions from different functional systems (as for example in functional harmonics 5 and 6) led us to hypothesize that functional harmonics provide a unifying explanation for two seemingly opposing perspectives of cortical organization: the gradiental perspective arguing that cortical organization is continuous on the one hand and the modular perspective stating that brain function emerges from modular organization of specialized brain regions on the other. We therefore explicitly tested whether functional harmonics fulfill the constraints posed by both of these views.

We first quantified the overall overlap between functional harmonic patterns and the brain regions (parcels) delineated by the HCP parcellation[3]. To this end, for each of the functional harmonics shown in Figure 2, we compared the within- and between-area-variability of each cortical region (see SI Figures 3-5), where a large difference between the within- and

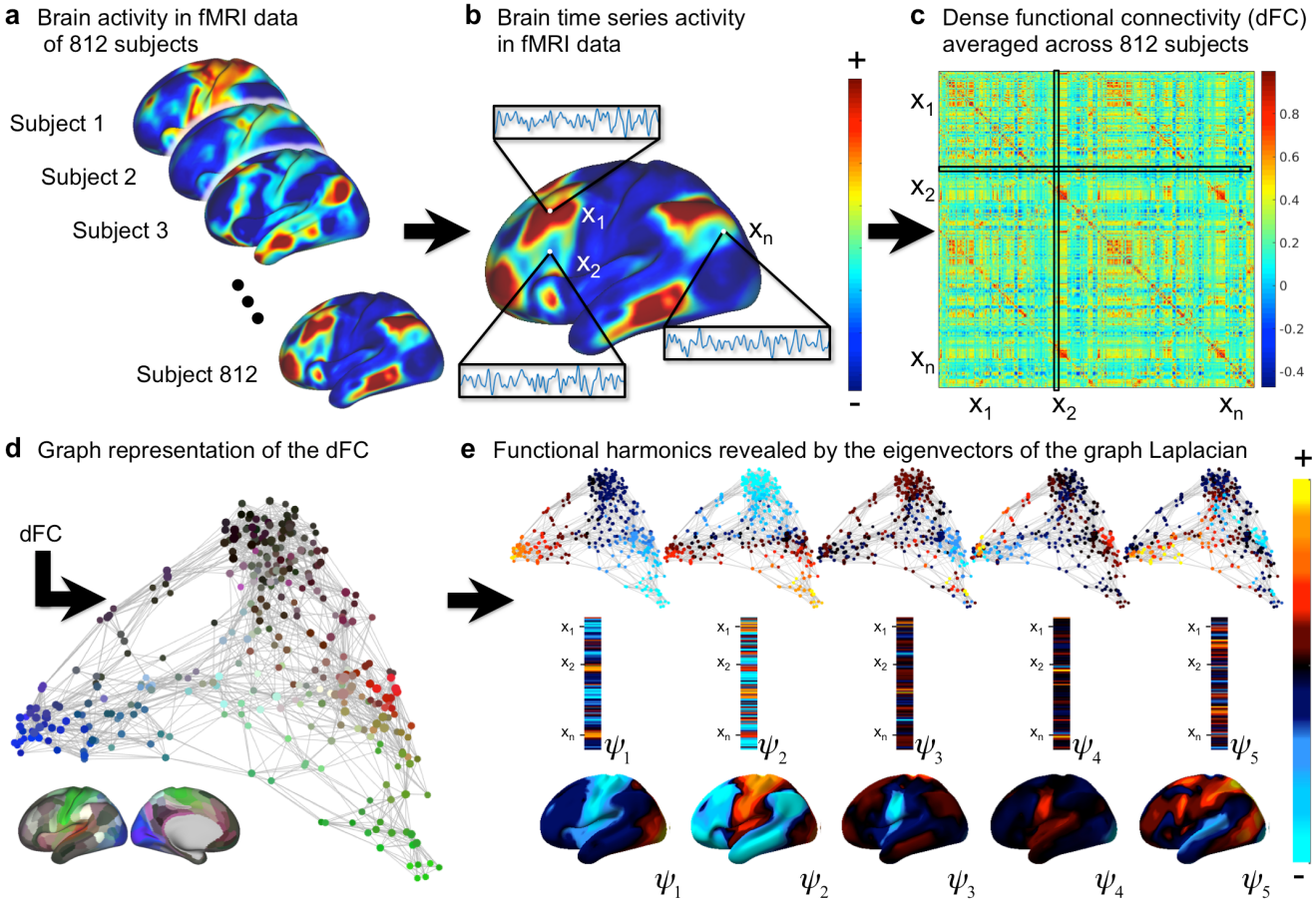

Figure 1. Workflow for the estimation of functional harmonics. a: Brain activity measured with functional magnetic resonance imaging (fMRI) in resting state for 820 subjects provided by the Human Connectome Project (HCP, 900 subjects data release)[40–47]. b: Illustration of brain time series activity of three representative vertices on the cortex ($x_1, x_2, \cdots, x_n$). c: The dense functional connectivity (FC) matrix computed from the temporal correlations between the time courses of each pair of vertices as shown in b averaged across 812 subjects. d: Representation of the dense FC as a graph, where the edges indicate strong correlations between the corresponding vertices. The anatomical location of the vertices are colour-coded[3]. e: Functional harmonics are estimated by the eigenvectors of the graph Laplacian computed on the graph representation of the FC. The first five functional harmonics ordered from the lowest to higher spatial frequencies are illustrated on the FC graph representation (top), in the eigenvector format as 64984 $\times$ 1 dimensional vectors (middle) and on the cortical surface (bottom). For illustrative purposes, the graph representations are shown for a parcellated version of the FC matrix using the HCP parcellation[3] in d and e. We note that the computation of the functional harmonics have been performed on the dense FC using 64984 $\times$ 64984 without using any parcellation.

between-area variability, indexed by a large silhouette value, indicates that that particular region is well-separated from the rest of the cortex[63]. We found an alignment between the isolines of the functional harmonics and parcel borders, as verified by significantly larger silhouette values for functional harmonics compared to harmonics computed on randomized connectivity graphs (values for functional harmonics between 0.67 and 0.87, maximum random value 0.20, significantly different with $p_{\text{corr}} < 0.05$ after Bonferroni correction, Monte Carlo tests; see Online Methods for details). For qualitative evaluation, the overlap between parcels and functional harmonics is shown in SI Figure 6.

In addition to the parcels delineated in the HCP parcellation[3], we investigated whether functional harmonics also capture somatotopy[15] and retinotopy[14], two major topographic mappings found in the brain. Topographic mappings represent sensory input on the cortical surface such that the relative positions of the receptors, which receive these inputs, are preserved. Five somatotopic sub-areas (in each hemisphere) as defined by the HCP[3] form a topographic map of the surface of the body on the cortex, i.e., the face, hands, eyes, feet, and trunk.

To quantify the degree to which each somatotopic sub-area is delineated within a particular functional harmonic, we again

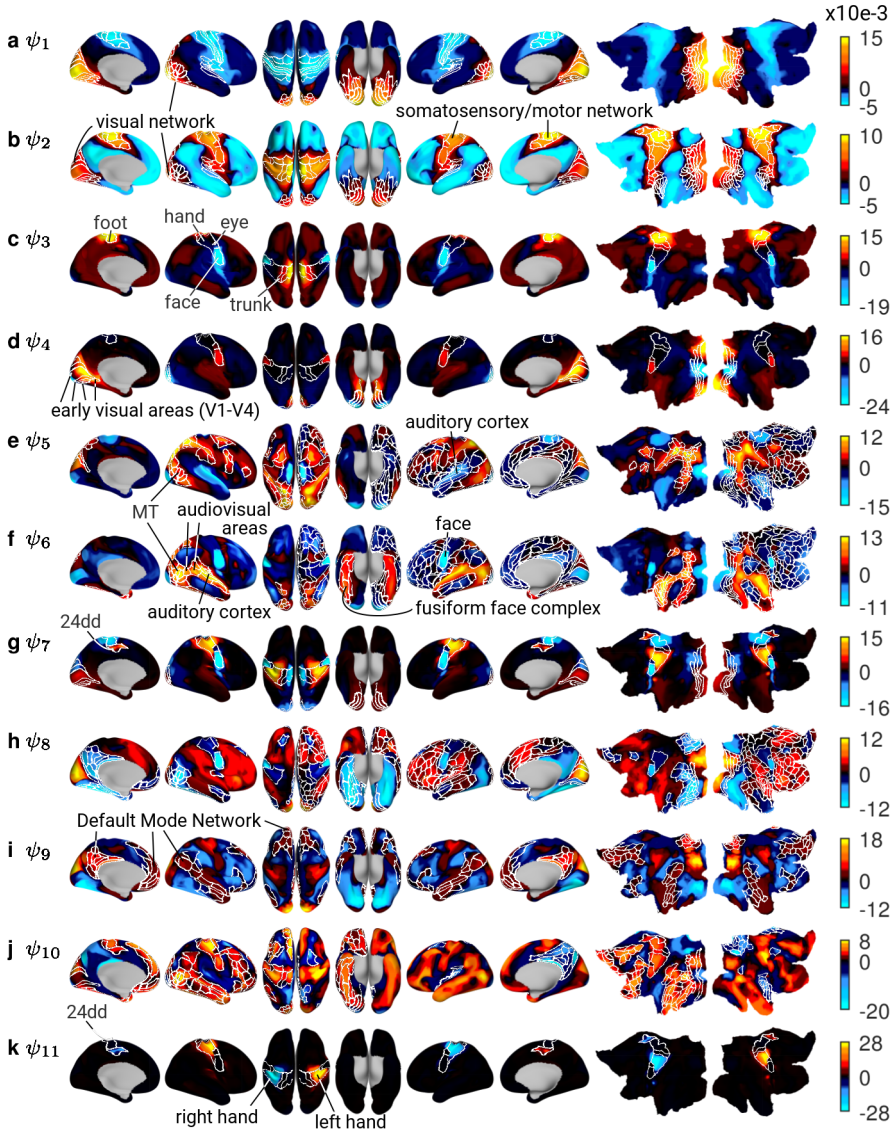

Figure 2. a-k: The first 11 non-constant harmonics plotted on the cortical surface. White lines show borders of HCP parcels. V1-V4: visual areas 1 to 4; MT: middle temporal visual area; 24dd: an area that contains a higher order representation of the hand; fusiform face complex: an area that responds specifically to images of human faces.

utilized the within- and between-area-variability as above, but applied specifically to the 10 somatotopic sub-areas (see SI Figure 7). We measured their separation both from the rest of the brain as well as from other somatotopic areas. We found that for all functional harmonics shown in Figure 2 except for the one with the lowest frequency that delineates the complete somatomotor cortex, at least one somatotopic region is significantly separated ($p_{\text{corr}} < 0.05$ after Bonferroni correction, Monte Carlo tests). This finding indicates that functional harmonics capture somatotopic organization in the cortex. Figure 3a illustrates the two-dimensional subspace formed by functional harmonics 3 and 11, which strikingly accounts for the precise mapping of the human body onto the somatotopic regions of the cortex (see SI Figure 1b-d for further examples).

We next investigated the presence of retinotopic mapping of early visual regions (V1-V4), where cortical representations of the visual field reflect the positions of the receptors such that each vertex within the patterns of functional harmonics is assigned an eccentricity (distance from the fovea) and an angle (top, bottom, left, right)[53]. To investigate the degree of agreement between the functional harmonics and the retinotopic mappings, we measured the correlation between eccentricity as well as polar angle maps and the functional harmonic patterns in V1-V4. We found significant correlations ($p_{\text{corr}} < 0.05$ after Bonferroni correction) between the retinotopic eccentricity map and all harmonics except functional harmonic 9; and between the retinotopic angular map and harmonics 1-4, 7-9, and 11. Examples of polar plots of the retinotopic gradients are shown in

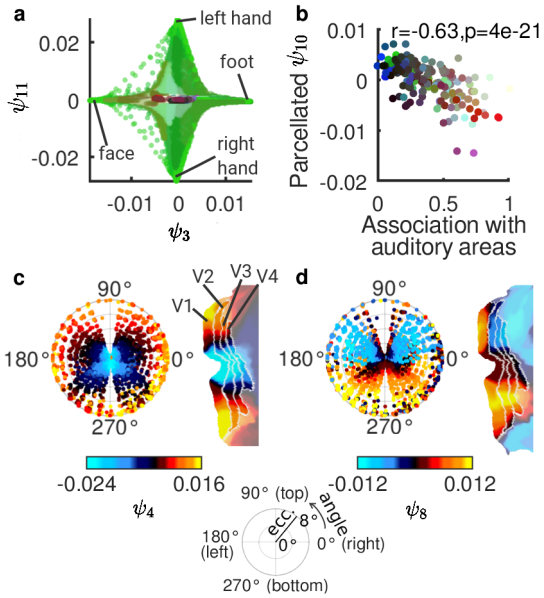

Figure 3. a: Functional harmonics 3 (ψ_3) and 11 (ψ_{11}) in their own space. The location of 4 somatotopic areas in this space is annotated. b: Correlation between the degree to which areas are related to auditory regions[3] and the value of functional harmonic 10 (ψ_{10}), averaged within each of the 360 parcels. The color code is taken from the parcellation in Glasser et al. (2016)[3], see also figure 1d. c and d: Retinotopies of functional harmonics 4 (c; ψ_4) and 8 (d; ψ_8). Each panel shows, on the left, the colors of the respective functional harmonic in early visual areas V1-V4 on a polar plot of eccentricity (distance in degree from the fovea) and angle on the visual field (see legend at the bottom of the figure). On the right, the respective functional harmonic is shown on a flat map of early visual cortex (left hemisphere). V1, V2, V3, V4: visual areas 1, 2, 3, 4.

Figure 3c, d (all polar plots available in SI Figure 8).

Besides the two major topographic mappings of the cortex, we observed that functional harmonic 10 captures the hierarchical organization of the auditory system. To quantify this agreement, we measured the correlation between the spatial pattern of functional harmonic 10 and the extent to which each area is associated with the auditory network in the resting state (degree of auditory involvement)[3]. We found a significant correlation ($r = -0.63$, $p = 4 \cdot 10^{-21}$) between functional harmonic 10 and the degree of auditory involvement of the functional areas (Figure 3b).

Functional harmonics are basis functions of human cognition

Considering the parallel between functional harmonics and the well-known Fourier basis, i.e. the fact that they both are defined as Laplacian eigenfunctions, the former applied to a one-dimensional domain with cyclic boundaries (a circle) and the latter to the communication structure of the human brain (dense FC matrix), the functional harmonics provide an extension of the Fourier basis to the communication structure of the human brain. As such, they provide per definition a frequency-specific function basis, in which any pattern of brain activity can be represented as a weighted combination of functional harmonics. Given the experimental evidence showing that resting state functional connectivity reflects connectivity during task[9–12], we hypothesized that functional harmonics provide building blocks of task activity measured on the cortex. In order to test this hypothesis, we reconstructed 47 group-level task maps provided by the HCP[52] from the functional harmonics (see Online Methods). The 47 maps are activation maps as well as contrasts derived from 7 groups of tasks (working memory, motor, gambling, language, social, emotional, relational - see Online Methods for summaries). The functional harmonic reconstruction yields a coefficient (weight) for each functional harmonic, quantifying how much it contributes to a certain task map. The set of all coefficients forms a spectrum equivalent to the power spectrum obtained from a Fourier transform, in this case the power spectrum of the functional harmonic basis.

We first tested whether it is possible to approximate task maps as superpositions of subsets of functional harmonics, linearly combining them in the order of their eigenvalues. We quantified the goodness of fit by measuring the distance between the original and the reconstructed task maps. Figure 4a shows the normalized reconstruction errors for all groups of tasks: The error drops from about 1.00 to about 0.40 when using the 11 exemplary harmonics of Figure 2, corresponding to 0.02% of the total functional harmonic spectrum. Figure 4b illustrates this for one specific task (working memory - body; see also SI Figures

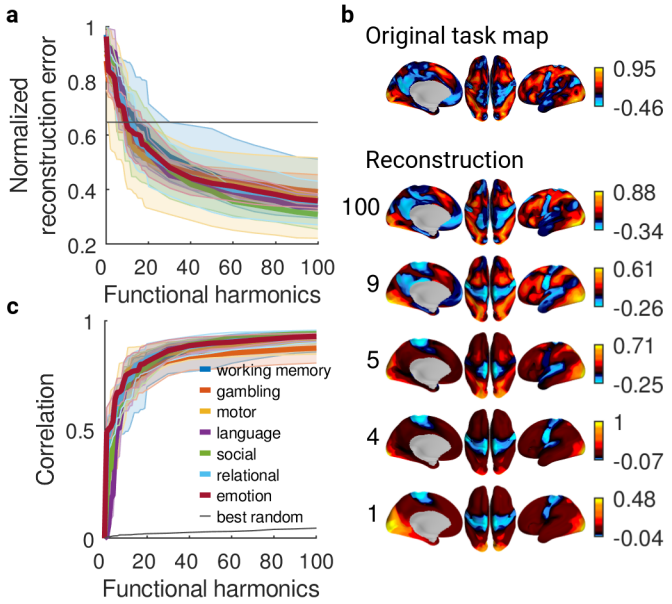

Figure 4. a: Reconstruction errors for all 7 task groups. Thick line: mean, the shaded area contains all values within that task group (all curves shown in SI Figure 9a); b: One example for a reconstruction using a working memory task. The top panel is the original task activation map (working memory - body), and subsequent panels use the number of harmonics indicated on the left to reconstruct it. c: Like a, but showing correlation between reconstructed and original task maps (all curves shown in SI Figure 9b).

10-16).

As a control, we performed 418 Monte Carlo simulations, in which we randomized the dense FC matrix while preserving the degree of each node. We computed the functional harmonics of each randomized connectivity matrix. This control still yields harmonic patterns emerging on the cortex computed as the eigenfunctions of the Laplacians of the randomized FC graphs, but these random harmonics are estimated from a random connectivity instead of the communication structure of the human brain. The black line in Figure 4a shows the lowest reconstruction error across all randomizations (0.65), for any number of functional harmonics between 0 (only the constant harmonic) and 100. When using 30 functional harmonics (0.05% of the functional harmonic spectrum), the reconstruction with the maximum reconstruction error across all 47 task maps still outperforms the best reconstruction using the randomized harmonic basis. As a complementary measure to the reconstruction error, we computed the correlation between the reconstructed and the original task activation maps, shown in Figure 4c. When using 9 or more functional harmonics, all task reconstructions significantly correlate with their original task map ($p_{\text{corr}} < 0.05$ after Bonferroni correction; maximum random correlation: 0.05, shown in black in Figure 4c; see Online Methods for details).

Given that functional harmonics constitute functionally relevant communication channels, we hypothesized that the task activation maps can be characterized by their power spectrum. Figure 5a, d and Figure 5b, e, show two examples of task activation maps and the corresponding normalized power of the first 11 non-constant functional harmonics, respectively, revealing how strongly each of the 11 functional harmonics shown in Figure 2 contributes to these particular task maps. For qualitative evaluation, we display the task activation maps reconstructed by superimposing functional harmonics in the order of their contribution strength for varying numbers of functional harmonics in Figure 5c, f (see also SI Figures 10-16). Across all 47 task maps that were evaluated, the functional harmonic which was the strongest contributor was always either the constant functional harmonic or one of the first 11 non-constant harmonics shown in Figure 2.

In order to evaluate the uniqueness of the functional harmonic power spectrum of each task activation map, we computed the distance between a given reconstructed map and all original task maps, resulting in a confusion matrix for each number of harmonics with maximum contribution. If task maps can indeed be characterized by their functional harmonics power spectra, the error should be minimal between a reconstruction and its corresponding task map compared to the error of the reconstruction of the other 46 task maps. The confusion matrices in Figure 5g-i show the pairs of the original and reconstructed task activation maps with the minimum distance when using 1, 4, and 40 functional harmonics with maximum contribution. Coloured squares mark the 7 task groups as in Figure 4. The proportion of unambiguously identified tasks in relation to the number of functional harmonics is shown in Figure 5j. We found that sparse representations using the 4 functional harmonics with the largest power for each task are sufficient to unambiguously characterize the seven task groups (Figure 5h), and 70% of all individual tasks.

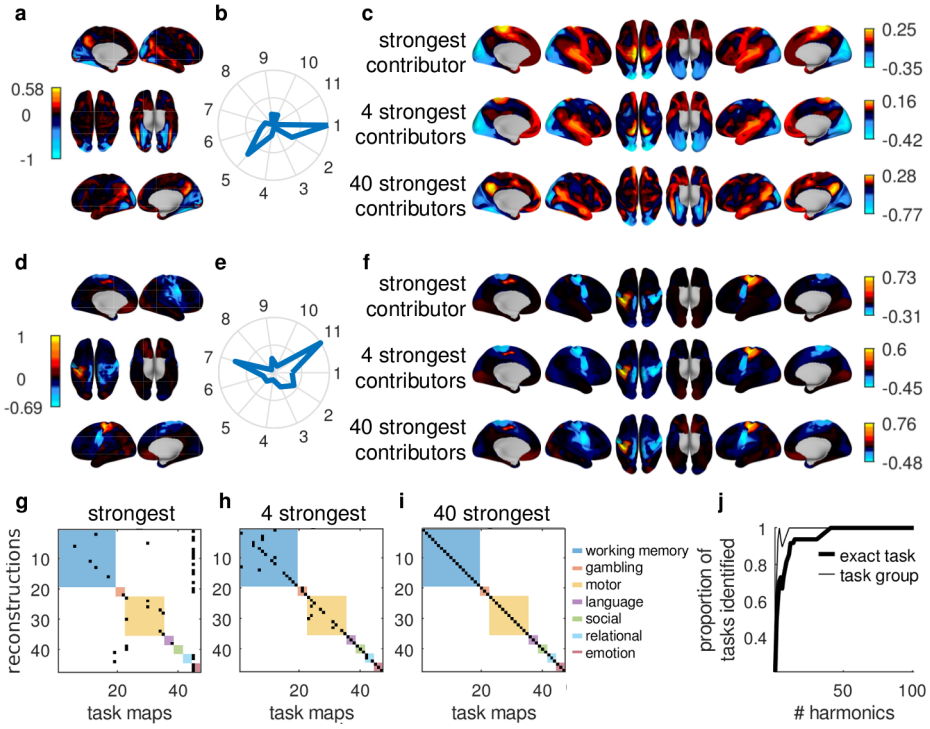

Figure 5. a: Map of the contrast between working memory (face) and average working memory from the HCP task dataset[52], b: Contributions (normalized coefficients of the graph Fourier transform) for the first 11 non-constant functional harmonics, c: Reconstruction of the task map in panel a when using the functional harmonic with the strongest contribution (highest coefficient) only, the four functional harmonics with the strongest contributions, and the forty functional harmonics with the strongest contributions. d-f: The same as a-c using the map of the contrast between motor (right hand) and average motor. g-i: Confusion matrices. Black entries mark the task map-reconstruction-pair which has the lowest reconstruction error, colored squares indicate the task group as in Figure 4. j: Proportion of reconstructions, for each number of harmonics, which have the minimum reconstruction error with their exact original task map (thick line) and a task map belonging to the same group of tasks as the original map (thin line).

When the 40 functional harmonics with maximum contribution are used, which corresponds to 0.1% of the complete spectrum of functional harmonics, all of the 47 task maps are correctly identified from their reconstructions (Figure 5i). The maximum number of correctly classified tasks was significantly larger for functional harmonics than for randomized harmonics (47 vs 4 correctly classified tasks, $p < 0.005$, Monte Carlo simulations with 418 trials).

Overall, our results demonstrate that that functional harmonics provide a novel functionally relevant representation, where the brain activity accompanying different tasks can be uniquely identified from the activation profiles of a small range of functional harmonics.

Discussion

We reveal a previously unknown principle of cortical organization by applying a fundamental principle ubiquitous in nature - harmonic modes - to the communication structure of the human brain. The resulting modes termed functional harmonics reveal a data-driven, frequency-specific function basis derived from the human resting state functional connectivity matrix and constitute the optimal mapping of the communication structure encoded in this matrix onto the cortex. Here, we demonstrate the meaning of the first 11 functional harmonics as brain's functional communication channels, which are distinctly separated and ordered in the frequency domain. In this view, functional harmonics provide a multidimensional representation of brain activity that is not confined to a certain spatial scale. In particular, the mechanism by which a brain region is able to fulfill a multitude of functions depending on the context is enabled by its simultaneous membership in several communication channels. Thus, functional harmonics unify the competing views that brain activity arises *either* from smoothly varying gradients *or* from the modular and specialized regions: specialized regions emerge from the interaction of functional harmonics across multiple dimensions. Hence our findings provide, to our knowledge, the first principle that unifies the gradiental and modular aspects and reveals the multi-dimensional nature of cortical organization.

Furthermore, by definition, functional harmonics are the extension of the well-known Fourier basis to the functional connectivity of the human brain. As such they provide a function basis to reconstruct any pattern of brain activity as superpositions of these harmonic patterns. We explicitly show that functional harmonics are building blocks of cognitive activity in the brain by characterizing a multitude of task activation maps from their functional harmonic reconstructions.

Considering that the principle of harmonic modes when applied to the *structural* connectivity of the human brain - the human connectome - have been shown to reveal the functional networks[31], our results point to the emergence of the same fundamental principle in multiple aspects of human brain function. Beyond the results presented here, functional harmonics suggest novel ways to understand the dynamics of the human brain in health and in pathology as well to explore individual differences within this multi-dimensional harmonic representation.

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Online Methods

Data

The data used in this study was acquired and made publicaly available by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University. All study protocols were approved by the Washington University institutional review board, and informed consent was obtained in all cases[40,41].

In this study, we used the dense functional connectivity (FC) matrix, which is part of the Human Connectome Project's 900 subjects data release[40–47]. It is available under db.humanconnectome.org/data/projects/HCP_1200[64]. Clicking on "812 Subjects, recon r227, Dense Connectome" will download the appropriate .zip-archive (user login necessary). The list of names of all the files used in this study is shown in Table 1. Note that in this release, many of the subjects are related to at least one other subject of the group. The group average functional connectivity matrix was obtained by correlating group-PCA eigenmaps from 812 out of the 900 subjects included in this release, which are the subjects that having completed all four sessions of 15-minute resting state fMRI.

For task reconstructions, we used data contained in the S1200 group average data release, which is available on www.humanconnectome.org/study/hcp-young-adult/document/extensively-processed-fmri-data-documentation, as "HCP_S1200_GroupAvg_v1 Dataset".

For the analyses involving retinotopic maps, we used data available on osf.io/bw9ec/ and described in Benson et al. (2018)[53]. The relevant file is named "prfresults.mat" and contains a variable "allresults" of dimensionality 91282 (grayordinates) $\times$ 6 (quantities) $\times$ 184 (181 subjects plus 3 different group averages) $\times$ 3 (model fits). We used only the quantities 'ang' and 'ecc', the first model fit, of the group average across all available subjects, which uses all available time points. See osf.io/bw9ec/wiki/home/ for details.

Data are encoded in CIFTI file format[40], which means that coordinates are defined on the cortical surface ("grayordinates"), i.e. using n vertices rather than voxels[47]. The file was read using connectome workbench functions[64] and converted to a single precision vector of length $(n \cdot n - n)/2$ (due to its symmetry) using Matlab[65]. We also excluded the medial wall. This reduced the size of the FC matrix in memory from 33 GB to approximately 6 GB, greatly easing subsequent computations. The loss in precision is negligible compared to the accuracy with which pairwise correlation can be estimated from noisy fMRI time courses.

For visualization purposes, we used the surfaces provided with the functional data.

Software

All data analysis was performed using MATLAB 2014b or 2017b, using also scripts and functions from the following freely available software packages:

- Fieldtrip version 20180903
- Connectome workbench (https://www.humanconnectome.org/software/connectome-workbench)
- CNM toolbox (https://www.mathworks.com/matlabcentral/fileexchange/45734-cnm)
- gifti toolbox (https://www.artefact.tk/software/matlab/gifti/)

Background: Functional Harmonics

The approach presented here relies on representing the human brain's communication structure (dFC) as a graph and estimating the eigenfunctions of graph Laplacian applied to this structure. The graph representation of the brain's communication structure $\mathscr{G} = (\mathscr{V}, \mathscr{E})$ is created by representing the vertices sampled form the gray matter cortical surface as the nodes $\mathscr{V} = \{v_i | i \in 1, \cdots, n\}$ with n being the total number of nodes ($n = 59.412$ in this study) and by representing the connections between the vertices as the edges $\mathscr{E} = \{e_{ij} | (v_i, v_j) \in \mathscr{V} \times \mathscr{V}\}$, which come from the connections in the dFC matrix. We represent this graph structure $\mathscr{G}$ by its $n \times n$ adjacency matrix $A = [a_{ij}]$ that is formed by connecting each node i to its k-nearest neighbours ($k = 300$ in this study) according to its correlations in the dFC matrix, i.e.:

$$a_{ij} = \begin{cases} 1 & c_{ij} \in \kappa_i, \forall j : 1 \leq j \leq n, j \neq i \\ 0 & c_{ij} \notin \kappa_i, \forall j : 1 \leq j \leq n, j \neq i \end{cases}, \tag{1}$$

where κ_i is the set of the k largest values in row i in the dFC matrix. In order to ensure A is symmetric, we also set $a_{ji} = 1$, if $a_{ij} = 1$. Defining $\mathbf{A}$ as such results in a symmetrical sparse binary matrix.

Table 1. Files used in our computations. All data was downloaded from the human connectome project database (db.humanconnectome.org/data/projects/HCP_1200) unless otherwise specified.

Purpose	file name	comment
Dense functional connectivity matrix	HCP_S900_820_rfMRI_MSMAll_groupPCA_d4500ROW... ..._zcorr.dconn.nii	
Medial wall index file	Human.MedialWall_Conte69.32k_fs_LR.dlabel.nii	
Cortical surfaces	S900.<hemisphere>.inflated_MSMAll.32k_fs_LR.surf, S900.<hemisphere>.flat.32k_fs_LR.surf.gii	replace <hemisphere> with "L" for left hemisphere, "R" for right
Cortical surface labels	Q1-Q6_RelatedValidation210.<hemisphere>. ... ...CorticalAreas_Final_Final_Areas_Group_Colors.32k_fs_LR.label.gii	replace <hemisphere> with "L" for left hemisphere, "R" for right
Borders	Parcellation: Q1-Q6_RelatedParcellation210. ... ...<hemisphere>.CorticalAreas.32k_fs_LR.border, Somatotopy: Q1-Q6_RelatedParcellation210. ... ...<hemisphere>.SubAreas.32k_fs_LR.border	replace <hemisphere> with "L" for left hemisphere, "R" for right
HCP atlas colours	atlas.mat from osf.io/bw9ec/	
Task maps	HCP_S1200_997_tfMRI_ALLTASKS_level2_cohensd... ..._hp200_s2_MSMAll.dscalar.nii www.humanconnectome.org/study/hcp-young-adult/document/extensively-processed-fmri-data-documentation	2 mm smoothing kernel
Retinotopy maps	prfresults.mat from osf.io/bw9ec/	using "group subject" (ID 999999) and full model fit
Yeo et al. 7-networks parcellation	RSN-networks.<hemisphere>.32k_fs_LR.label	replace <hemisphere> with "L" for left hemisphere, "R" for right

Then we estimate the graph Laplacian defined as

$$\mathbf{L}_{\mathscr{G}} = \mathbf{D} - \mathbf{A} \quad , \tag{2}$$

where $\mathbf{A}$ is the adjacency matrix as defined above, and $\mathbf{D}$ is the degree matrix, which is defined as a diagonal matrix with diagonal elements

$$d_{ii} = \sum_{j=1}^{n} a_{ij} \quad . \tag{3}$$

As such, the degree matrix $\mathbf{D}$ contains each node's degree in its diagonal. Finally, we estimate the functional harmonics as the eigenfunctions $\Psi = \{\psi_1, \psi_2, \cdots, \psi_n\}$ by solving:

$$\mathbf{L}_{\mathscr{G}} \psi_i = \lambda_i \psi_i, \quad i \in \{0, 1, \cdots, n\} \quad , \tag{4}$$

where ψ_i are the $n \times 1$ eigenvectors and λ_i are the corresponding eigenvalues.

Monte Carlo simulations

For statistical tests, we perform comparisons against a randomised connectivity graph. For randomization, we use an algorithm described in Molloy et al. (1995)[66] and adapt an implementation contained in the CNM toolbox (https://ch.mathworks.com/matlabcentral/fileexchange/45734-cnm). The randomization is performed at the level of the sparse nearest neighbor graph. First, all edges are "cut", producing vertices that have as many "stubs" as they had connections. These stubs are then randomly reconnected, effectively preserving the degree of each node. Random harmonic basis functions were then obtained from the resulting nearest neighbour graphs as for the original FC matrix, as described above. We produced $(1/\alpha - 1) \cdot H$ randomizations, where $\alpha = 0.05$ and $H = 22 = 11 \cdot 2$ since we tested the first 11 functional harmonics shown in Figure 2 and performed two separate sets of tests (average silhouette value over the whole cortex as well as maximum modified silhouette value over all somatotopic regions; see below).

Silhouette values

To test whether isolines of the functional harmonics follow the boundaries of the parcels as defined in the HCP parcellation[3], we compute the silhouette value[63] of each functional harmonic as:

$$S = \frac{1}{N} \sum_i (M_{\text{between}}(i) - M_{\text{within}}(i)) / \max(M_{\text{between}}(i) - M_{\text{within}}(i)) \quad , \tag{5}$$

where $M_{\text{between}}(i)$ is the average Euclidean distance between vertices belonging to a parcel i and vertices belonging to all other parcels, while $M_{\text{within}}(i)$ is the average distance between vertices within the parcel i. If all vertices belonging to a parcel i have the same value, and at least some vertices outside the parcel i have different values, then $M_{\text{between}}(i) > 0$, $M_{\text{within}}(i) = 0$ and $S(i) = 1$. By averaging over the silhouette values of all parcels, one obtains a measure of how well the data fit the parcellation. Note that we replaced the somatosensory/motor core areas 1, 2, 3a, 3b, and 4 with the somatotopic sub-areas given by the HCP[3] for a more detailed evaluation.

To evaluate the somatotopic organization of the functional harmonics, we use a measure that was similar to the silhouette value, but adapted to measure the separation from the rest of the cortex *and* from other somatotopic areas.

$$S_{\text{som}} = \max_{\text{som}} \left((M_{\text{between,som}} + M_{\text{between}}) / \max(M_{\text{between,som}}, M_{\text{between}}) \cdot M_{\text{between,som}} \right) \quad , \tag{6}$$

where $M_{\text{between,som}}$ is the average Euclidean distance between vertices belonging to a somatotopic area and all other vertices belonging to all other somatotopic areas. The maximum is taken over the somatotopic areas. The first term of the equation is between 1 and 2 and is close to 2 if both $M_{\text{between,som}}$ and M_{between} are equal.

Task maps

We used group-averaged task activation maps provided with the S1200 group average data release of the HCP (see Table 1, www.humanconnectome.org/study/hcp-young-adult/document/extensively-processed-fmri-data-documentation). Here we provide a summary of the tasks that form part of the HCP task battery[52]. There are 7 groups of tasks: working memory, motor, gambling, language, social, emotional, relational. Subjects performed all tasks in two separate sessions (working memory, gambling, and motor in the first session, language, social cognition, relational processing, and emotion processing in the second).

Working memory. Four different stimulus types were used, presented in separate blocks: pictures of faces, places, tools and body parts. Two different task types were used: a 2-back working memory task, where subjects had to respond if a stimulus matched that two trials back, and a 0-back working memory task, where subjects had to respond whenever a single stimulus returned that was presented at the beginning of the block. This results in a total of 19 different working memory task maps, consisting of 14 activation maps (such as 0-back, 2-back, face, body, etc.) and 5 contrasts (between the two task types, between each stimulus type and the average across all stimuli, etc.).

Motor. Visual cues indicated whether participants should move their left or right fingers, left or right toes, or move their tongue. The goal was to identify the motor areas that correspond to these five body parts. This results in 26 different task maps (7 activation maps for 5 body parts plus visual cue plus average, and 6 contrast maps).

Gambling. (Incentive processing.) Subjects played a game in which they could win or lose money. The game was to guess whether the number on a "mystery card" that could range between 1 and 9 would be less or more than 5. The numbers were given after subjects made their guess and were chosen according to the trial type: "win" - the number would correspond to their guess and they would win 1$; "neutral" - the number would equal 5 and they would neither win nor lose any money; "loss" - the number would not correspond to the guess and participants would lose $0.50. Separate blocks are used in which trials are either mostly win or mostly lose, resulting in two conditions, punish and reward. This results in 3 different task maps (2 activation maps, i.e. one for each condition, and 1 contrast).

Language. Two different task types were used, "story" and "math". "Story" consisted of participants listening to 5-9 sentences of a story, and answering a 2-alternative forced choice question thereafter. "Math" required participants to solve simple addition and subtraction problems. The two task types are similar in terms of auditory input and attentional load, but different in terms of semantic and numerosity related processing. As for gambling, the two task types result in 3 task maps (2 activation, 1 contrast).

Social. (Theory of Mind, TOM.) Subjects viewed videos of objects (squares, circles, triangles) that moved around in one of two ways: "Random" - there was no interaction between the objects, or "TOM" - the objects moved as if they were reacting to the other objects' "thoughts and feelings". They then had to judge whether the objects were interacting or not, or respond with "not sure". As with gambling and language, the two task types result in 3 task maps (2 activation, 1 contrast).

Emotional. Subjects viewed one of two types of stimuli, "faces" or "shapes", and had to decide which of two stimuli presented at the bottom of the screen matched the stimulus at the top of the screen. The faces included emotional stimuli, i.e. angry or fearful expressions. Again, the two task types result in 3 task maps (2 activation, 1 contrast).

Relational. There were two conditions, "match" and "relational". In all cases, stimuli can have one of six shapes combined with one of six textures. In the "match" condition, which served as a control condition, two shapes were presented at the top and one at the bottom of the screen. A word ("shape" or "texture") that appears in the middle of the screen instructs subjects to decide whether the bottom stimulus matches either of the top stimuli in the dimension indicated by the word. In the "relational" condition, two stimuli are presented each at the top and at the bottom of the screen, with no word in the middle. Instead, participants have to determine themselves across which dimension the top pair differs, and, subsequently, indicate whether the bottom pair differs over the same dimension. Again, the two task types result in 3 task maps (2 activation, 1 contrast).

Task maps were computed using FSL's FEAT and FLAME[67,68] and conducting a between-subject ("level 2") analysis, resulting in effect sizes (Cohen's d). We used the task maps with minimal smoothing (2mm total smoothing); see 1200 subjects data release reference manual, pp. 45-54 and 100-104.

Reconstructing the task maps from functional harmonics

The spatial pattern of each task map on on the cortex $\mathbf{s}(v)$ was decomposed into and reconstructed from the functional harmonics $\Psi = \{\psi_k\}_{k=1}^{n}$ as:

$$\hat{\mathbf{s}} = \alpha_1 \psi_1 + \alpha_2 \psi_2 + \cdots + \alpha_n \psi_n = \sum_{k=1}^{n} \alpha_k \psi_k(v), \tag{7}$$

where the coefficient α_k of each functional harmonic ψ_k was estimated by projecting the task map $\hat{\mathbf{s}}(v)$ onto that particular harmonic ψ_k. As such α_k are estimated as:

$$\alpha_k = \langle \hat{\mathbf{s}}, \psi_k \rangle \quad . \tag{8}$$

Then, each task map is reconstructed using Eq. 7. In this study, we limit our reconstructions to using a maximum of 100 non-constant functional harmonics ($n = 101$).

For a reconstruction $\mathbf{s}^*{}_{(m)}$, where m indicates a binary vector of dimensionality 101×1 which contains ones for harmonic basis functions that are used in the reconstruction and zeros otherwise, we then compute the reconstruction error as:

$$\mathrm{RE}_{(m)} = \sqrt{\sum_i (s_i - s^*_{(m),i})^2 / \sum_i s_i^2} \tag{9}$$

We also computed the Pearson correlations between $\mathbf{s}$ and $\mathbf{s}^*{}_{(m)}$. For comparing the correlations between task maps and reconstructions obtained from real functional harmonics versus randomized connectivity harmonics, we considered the number of comparisons to be $\mathrm{nC} = \mathrm{nTasks} \cdot \mathrm{nLevels}$, where the number of tasks equals 47 and the number of levels refers to the different numbers of harmonics used in the reconstructions, i.e. 0, 1, 2, 3, ..., 20, 30, 40, ..., 100, in 29 levels. From this we obtained a corrected alpha level of $\alpha_{\mathrm{corr}} = 0.05/\mathrm{nC}$, and we computed the critical value as Fisher's z-transform of the correlation which a sample has to exceed in order to be significantly higher than the random correlation:

$$z_{\mathrm{crit}} = \frac{z_\alpha \cdot (\sqrt{\frac{1}{N_1-3} + \frac{1}{N_2-3}})}{z_{\mathrm{rand}}} \tag{10}$$

We obtain $z_{\mathrm{crit}} = 0.44$, which corresponds to a minimum required empirical correlation of 0.41, with $N_1 = N_2 = 59.412$ (the number of vertices that contribute to the correlation values), $z_\alpha = 0.438$ (the inverse Student's t distribution with $N_1 = N_2 = 59.412$ degrees of freedom evaluated at $1 - \alpha_{\mathrm{corr}}$), and $z_{\mathrm{rand}} = \mathrm{atanh}(0.05)$ (Fisher's z-transform of the maximal random correlation between any reconstruction - with any number of functional harmonics - and any task).

Visualization

Somatotopic areas. In the visual and somatosensory/motor cortices, functional harmonics are rather determined by retinotopy and somatotopy than by anatomical or microstructural features. For the former, somatotopic areas occupy exactly the same surface area as the sensorimotor core areas, 1, 2, 3a, 3b, and 4. We therefore replaced, where appropriate, the borders of the HCP parcellation by the borders of the five somatotopic regions.

Parcel borders for visualization. In order to discuss the meaning of the functional harmonics, we show borders of certain parcels on the cortical surfaces (Figure 2). We used three different methods to select which borders to show. First, for some functional harmonics, it was feasible to select these areas manually (for example, early visual areas in functional harmonic 4, somatotopic areas in functional harmonics 3 and 4). The anatomical supplementary information from Glasser et al. (2016)[3] uses a functional grouping of many regions that we often used as a guideline, for instance to distinguish between early and association auditory cortex. Second, for some functional harmonics (for instance, functional harmonics 1 and 2), we show the borders of parcels that belong to resting state networks as defined by Yeo et al. (2011)[48]. The 7-network parcellation is provided by the HCP, which does not perfectly overlap with the HCP parcellation. We adjusted the network borders slightly to align the network borders to follow those of the parcels defined in HCP. Thereby we assigned each parcel to the RSN with which it had the most overlap. Third, some functional harmonics are too complex to manually select areas or networks (namely, functional harmonics 5, 6, 8, and 10). Here we employed simple k-means clustering on the functional harmonic, using k=2 (functional harmonics 5, 6, and 8) or k=3 (functional harmonic 10). To obtain meaningful clusters in the somatosensory/motor cortex, we again replaced the sensorimotor core regions 1, 2, 3a, 3b and 4 with the somatotopic areas. For this purpose, we used vertices within the core regions and re-assigned them to the somatotopic areas based on their distances to the sub-area borders.

Author contributions statement

S. A. and K. G. designed the methodology and the analysis. J. P. and G. D. contributed to the design of the study. M. L. K. contributed to design of the methodology and the statistical analysis. M. L. K. and P. H. aided in the interpretation of the results. S. A., K. G. and M. L. K. wrote the manuscript. All authors reviewed the manuscript.

Data availability

All data generated in this study are available from the corresponding author upon reasonable request.

Code availability

All custom scripts used in this study are available from the corresponding author upon reasonable request.

Additional information

Competing financial interests The authors declare no competing financial interests.