Intrinsic timescales as an organizational principle of neural processing across the whole rhesus macaque brain

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Abstract
Hierarchical temporal dynamics are a fundamental computational property of the brain; however, there are no whole-brain, noninvasive investigations into timescales of neural processing in animal models. To that end, we used the spatial resolution and sensitivity of ultra-high field fMRI to probe timescales across the whole macaque brain. We uncovered within-species consistency between timescales estimated from fMRI and electrophysiology. Crucially, we were not only able to demonstrate that we can replicate existing electrophysiological hierarchies, but we extended these to whole brain topographies. Our results validate the complementary use of hemodynamic and electrophysiological intrinsic timescales, establishing a basis for future translational work. Second, with those results in hand, we were able to show that one facet of the high-dimensional FC topography of any region in the brain is closely related to hierarchical temporal dynamics. We demonstrated that intrinsic timescales are organized along spatial gradients that closely match functional connectivity gradient topographies across the whole brain. We conclude that intrinsic timescales are an unifying organizational principle of neural processing across the whole brain.

Author Contributions
Conceptualization: AMGM, AZ, SRH, JZ, ; Methodology: AMGM, JZ; Software: AMGM, JZ; Resources: SRH, JZ; Investigation: AMGM, SRH, JZ; Data curation: JZ; Formal Analysis: AMGM, JZ; Writing: AMGM, AZ, KU, SRH, JZ; Funding acquisition: AZ, KU, SRH, JZ.

Declaration of Interests
The authors declare no competing interests.

1. Introduction

Recent work supports the idea that the neural processing is organized over multiple timescales (Cavanagh, Hunt, & Kennerley, 2020; Hasson, Yang, Vallines, Heeger, & Rubin, 2008; Honey et al., 2012; Kiebel, Daunizeau, & Friston, 2008; Murray et al., 2014; Raut, Snyder, & Raichle, 2020; Soltani, Murray, Seo, & Lee, 2021). Hierarchical temporal dynamics are a fundamental computational property of the brain—fast changing sensory input is encoded by the fast dynamics of sensory areas, which is in turn integrated into temporally extended representations encoded by the slower dynamics of higher-order areas (Cavanagh et al., 2020; Raut et al., 2020; Soltani et al., 2021). Temporal integration and information processing over multiple timescales are crucial for understanding how the brain deals with the complexity of the real world (Zimmermann, Glimcher, & Louie, 2018), hence, understanding whole brain temporal dynamics is highly important.

As one moves from sensory to associative areas, neural processing reflects a hierarchy of progressively longer "temporal receptive windows" (TRW)—defined as the length of time during which an area accumulates information during task performance (Hasson et al., 2008). In other words, the range of the TRW of each area reflects its functional role, with sensory areas having short TRWs, to enable fast sensory processing, and associative areas having longer TRWs, allowing them to process information unfolding over longer periods of time. Not only does neural processing display these timescales during task performance, but we now know that temporal specialization arises from a region's intrinsic dynamics, that is, temporal dynamics that are present even in the absence of direct sensory stimulation. This was first described by Murray and colleagues (2014) analyzing action potentials of single neurons in the macaque. They showed that timescales of baseline neuronal activity vary across cortical areas, revealing a hierarchical progression from fast timescales in sensory areas, to slower timescales in association areas. These intrinsic fluctuations in the neural signal, also described as intrinsic neural timescales (INTs), are thought to set the duration over which brain regions integrate inputs (Murray et al., 2014). They are hypothesized to be the result of multiple neuronal mechanisms, including local dynamics and recurrent connectivity (Murray et al., 2014; Soltani et al., 2021; Watanabe, Rees, & Masuda, 2019).

Additional studies have replicated and extended the INT hierarchy, reinforcing the idea that brain regions exhibit unique timescales in their intrinsic activity, which reflect functional specialization in terms of temporal integration (Cavanagh, Wallis, Kennerley, & Hunt, 2016; Cirillo, Fascianelli, Ferrucci, & Genovesio, 2018; Fascianelli, Tsujimoto, Marcos, & Genovesio, 2019; Murray et al., 2014; Ogawa & Komatsu, 2010; Rossi-Pool et al., 2021, Maisson et al., 2021). The concept of INT hierarchy has even been extended to subcortical regions—specifically the basal ganglia (Nougaret, Fascianelli, Ravel, & Genovesio, 2021). Moreover, a large-scale network model, based on anatomical connectivity and the strength of local recurrent connectivity, has been used to successfully reproduce the temporal hierarchy (Chaudhuri, Knoblauch, Gariel, Kennedy, & Wang, 2015). This suggests that anatomical connectivity is closely related to INTs.

Alterations in hierarchical INT patterns can result in cognitive and behavioral abnormalities (Watanabe et al., 2019; Wengler, Goldberg, Chahine, & Horga, 2020; Zilio et al., 2021). For example, abnormal INT patterns have been associated with core symptoms of high-functioning individuals with Autism Spectrum Disorder (Watanabe et al., 2019). Likewise,

delusions and hallucinations are associated with INT alterations at different hierarchical levels, leading to symptom-specific changes in hierarchical INT gradients (Wengler et al., 2020). Hence, investigations into INTs have the potential to clarify hierarchical dysfunction in whole brain dynamics in neuropsychiatric disorders.

Traditionally, INTs have been investigated using invasive electrophysiology, which is not suited to uncover whole-brain dynamics. It is also challenging to collect in humans, particularly for large datasets (as would be needed to assess differences across populations). One way to overcome this problem is using functional magnetic resonance imaging (fMRI), which offers whole brain coverage and can be performed across species and in larger sample sizes. However, it is not yet clear whether hemodynamic INTs derived from fMRI reflect similar neural phenomena as those derived from electrophysiology. To clarify this issue, electrophysiological and hemodynamic INTs must be compared directly within the same species. To that end, recent advancements in non-human primate (NHP) neuroimaging, significantly boosting signal-to-noise ratios (Yacoub et al., 2020), make it possible to study hemodynamic INTs in the macaque brain. Moreover, taking advantage of the whole-brain coverage of fMRI, we are investigating INT topography. This is important since more recent work has shown that there is significant heterogeneity within regions (Cavanagh et al., 2020; Cirillo et al., 2018; Nougaret et al., 2021), while initial investigations had assigned INTs to cortical regions as a whole,

In addition to INTs, gradients of functional connectivity (FC) can also describe the functional architecture of neural processing (Haak, Marquand, & Beckmann, 2018; Vos de Wael et al., 2020). Gradient approaches map macroscale brain features to low dimensional manifold representations (Vos de Wael et al., 2020). Gradient mapping has the potential to uncover overlapping functional topographies by treating the high dimensional connectivity structure as a spatial variance decomposition problem. Notably, this approach finds patterns in the high-dimensional FC similarity structure that describe the spatial direction of maximum FC variance. For example, areas in the early visual cortex are known to exhibit at least two gradual modes of functional change (i.e., eccentricity and polar angle maps), which can be successfully retrieved from resting-state FC via gradient mapping (Haak et al., 2018). The existence of multiple overlapping principles of topographic organization is likely a general property of the whole brain (Haak et al., 2018; Harvey, Dumoulin, Fracasso, & Paul, 2020; Jbabdi, Sotiropoulos, & Behrens, 2013; Marquand, Haak, & Beckmann, 2017; Przeździk, Faber, Fernández, Beckmann, & Haak, 2019). Here, we carry out an investigation into the multi-dimensional functional architecture of the macaque brain by probing its spatial and temporal intrinsic dynamics. This allows us to achieve several significant goals. First, we are able to relate fMRI hemodynamic timescales to the gold standards of electrophysiology within the same species. Second, with those results in hand, we are able to show that one facet of the high-dimensional FC topography of any region in the brain is closely related to INT topography. We show that the hierarchical intrinsic dynamics of neural processing manifest into gradients of INTs and FC which follow the same gradual topographical arrangement. In sum, we reliably describe one facet of the macroscale functional organization of the brain, with respect to spatial and temporal dynamics.

2. Materials and methods

2.1. Animal preparation

We obtained data from 9 adult macaque monkeys (*Macaca fascicularis*: 5 female, and *Macaca mulatta*, 3 male and 1 female). Weights ranged from 3.0 kg to 9.4 kg. Experimental procedures were carried out in accordance with the University of Minnesota Institutional Animal Care and Use Committee and the National Institute of Health standards for the care and use of NHPs. All subjects were fed *ad libitum* and pair-housed within a light and temperature controlled colony room. Animals were not water restricted. None of the subjects had any prior implant or cranial surgery. Animals were fasted for 14-16 hours prior to imaging.

On scanning days, anesthesia was first induced by intramuscular injection of atropine (0.5 mg/kg), ketamine hydrochloride (7.5 mg/kg) and dexmedetomidine (13 ug/kg). Subjects were transported to the scanner anteroom and intubated using an endotracheal tube. Initial anesthesia was maintained using 1.0-2% isoflurane mixed with oxygen (1L/m during intubation and 2L/m during scanning to compensate for the 12m length of the tubing used). For functional imaging, the isoflurane level was lowered to 1%.

Subjects were placed onto a custom-built coil bed with integrated head fixation by placing stereotactic ear bars into the ear canals. The position of the animal corresponds to the sphinx position. Experiments were performed with animals freely breathing. An initial bolus injection of 1.5ug/kg fentanyl was administered IV followed by a continuous administration of 3ug/kg/hr using a syringe pump. Rectal temperature (~99.6F), respiration (10-15 breaths/min), end-tidal CO2 (25-40), electrocardiogram (70-150 bpm) and SpO2 (>90%) were monitored using an MRI compatible monitor (IRADIMED 3880 MRI Monitor, USA). Temperature was maintained using a circulating water bath as well as chemical heating pads and padding for thermal insulation.

2.2. Data acquisition

All data were acquired on a passively shielded 10.5 Tesla, 88 cm diameter clear bore magnet coupled to Siemens gradients (“SC72” body gradients operating at a slew rate of 200 mT/m/s, and 70 mT/m maximal strength) and electronics (Magnetom 10.5T Plus) (Siemens, Erlangen, Germany). Within the gradient set and the bore-liner, the space available for subject insertion had a 60 cm diameter.

The 10.5T system operates on the E-line (E12U) platform which is directly comparable to clinical platforms (3T Prisma/Skyra, 7T Terra). As such, the user interface and pulse sequences were identical to those running on clinical platforms. A custom in-house built and designed RF coil with an 8-channel transmit/receive end-loaded dipole array of 18 cm length (individually) combined with a close-fitting 16-channel loop receive array head cap, and an 8-channel loop receive array of 50 × 100mm size located under the chin (Lagore et al., 2021). The size of 14 individual receive loops of the head cap was 37 mm with 2 larger ear loops of 80 mm - all receiver loops were arranged in an overlapping configuration for nearest neighbor decoupling. The resulting combined 32 receive channels were used for all experiments and supported 3-fold acceleration in phase encoding direction. The coil holder was designed to be a semi-stereotaxic instrument holding the head of the animal in a centered sphinx position via customized ear bars. The receive elements were modelled to adhere as close to the surface of the animal's skulls as

possible. Transmit phases for the individual transmit channels were fine-tuned for excitation uniformity for one representative mid-sized animal and the calculated phases were then used for all subsequent acquisitions. Magnetic field homogenization (B0 shimming) was performed using a customized field of view with the Siemens internal 3D mapping routines. Multiple iterations of the shims (using the adjusted FOV shim parameters) were performed and further fine adjustment performed manually on each animal. Third order shim elements were ignored for these procedures.

In all animals a B1+ (transmit B1) fieldmap was acquired using a vendor provided flip angle mapping sequence (example result in Sup. Fig. 9) and then power calibrated for each individual. Following B1+ transmit calibration, 3-5 averages (23 minutes) of a T1 weighted magnetization prepared rapid acquisition gradient echo protocol (3D MP-RAGE) were acquired for anatomical processing (TR = 3300 ms, TE = 3.56 ms, TI = 1140 ms, flip angle = 5°, slices = 256, matrix = 320 × 260, acquisition voxel size = 0.5 × 0.5 × 0.5 mm3). Images were acquired using in plane acceleration GRAPPA = 2. A resolution and FOV matched T2 weighted 3D turbo spin echo sequence (variable flip angle) was run to facilitate B1 inhomogeneity correction.

Before the start of the functional data acquisition, five images were acquired in both phase encoding directions (R/L, L/R) for offline EPI distortion correction. Five - six runs of 700 continuous 2D multiband (MB) EPI (Moeller et al., 2010; Setsompop et al., 2012; Uğurbil et al., 2013) functional volumes (TR = 1110 ms; TE = 17.6 ms; flip angle = 60°, slices = 58, matrix = 108 × 154; FOV = 81 × 115.5 mm2; acquisition voxel size = 0.75 × 0.75 × 0.75 mm3) were acquired. Images were acquired with a left-right phase encoding direction using in plane acceleration factor GRAPPA = 3, partial Fourier = 7/8th, and MB or simultaneous multislice factor = 2. Since macaques were scanned in sphinx positions, the orientations noted here are what is consistent with a (head first supine) typical human brain study (in terms of gradients) but translate differently to the actual macaque orientation.

2.3. Image preprocessing

Image processing was performed using a custom pipeline relying on FSL (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012), ANTs (Avants et al., 2014; Avants, Tustison, Wu, Cook, & Gee, 2011), AFNI (Cox, 1996) and a heavily modified CONN (Whitfield-Gabrieli and Nieto-Castanon, 2012) toolbox. Images were first motion corrected using *mcflirt* (registration to the first image). Motion parameters never exceeded 0.5 mm or 0.4° rotation except in one run of one animal, which was discarded (the animal experienced anesthesia-induced emesis during the last run). Images were slice time corrected and EPI distortion corrected using *topup*. High magnetic fields and large matrix sizes are commonly associated with severe EPI distortions. Anatomical images were nonlinearly warped into the “National Institute of Mental Health Macaque Template” (NMT) (Seidlitz et al., 2018) template using ANTs and 3DQwarp in AFNI. The distortion correction, motion correction and normalization were performed using a single sinc interpolation. Images were spatially smoothed (FWHM = 2 mm), linear detrended, denoised using a linear regression approach including heart rate and respiration, as well as a 5 component nuisance regressor of the masked white matter and cerebrospinal fluid and band-pass filtering (0.008 - 0.09 Hz) (Hallquist, Hwang, & Luna, 2013).

2.4. INTs

Based on previous studies (Murray et al., 2014; Watanabe et al., 2019), INTs were calculated by estimating the magnitude of the autocorrelation of the preprocessed functional data. At the single-subject level, the INT of each voxel was quantified as follows. For each run, the autocorrelation function (ACF) of each voxel's fMRI signal was estimated. The ACF is the correlation of y_t (time series) and y_{t+k} (lagged time series), where k represents the time lag in steps of TR. Next, the sum of ACF values was calculated in the initial positive period. The upper limit of this period was set at the point where the ACF first becomes negative as the time lag increases. The result was used as an index of the INT of the brain region. At the single-subject level, the number of INT maps was dependent on the number of functional runs. The maps were not smoothed, because individual variation in FC gradients and INTs has been shown to have functional significance (Przeździk et al., 2019; Watanabe et al., 2019).

To examine the correspondence between fMRI-based and electrophysiology-based INT hierarchies, the values of individual voxels were averaged within areas. The areas were defined based on the Cortical Hierarchy Atlas of the Rhesus Macaque (CHARM) (Jung et al., 2021) and Subcortical Atlas of the Rhesus Macaque (SARM) (Hartig et al., 2021) to closely match the corresponding electrophysiological recording sites (see Supplementary Table 1). In some cases, since the CHARM parcellation did not match the recording sites, the regions of interest (ROIs) were drawn.

Stability and similarity

The intra-subject stability was quantified by calculating the pairwise correlation (i.e., Pearson's r) between the runs. The individual stability score was computed by averaging the Fisher's Z-transformed correlation coefficients across pairwise comparisons. For every subject, the maps were averaged across runs to quantify the inter-subject similarity. The individual similarity score was computed by averaging the subject's Fisher's Z-transformed correlation coefficients with all the other subjects.

To quantify the stability of the hierarchies, they were re-computed for groups of four subjects. The resulting ranking was correlated (i.e., Spearman's Rank correlation) with the group-level ordering of the cortical/subcortical regions. To estimate the stability score, this procedure was repeated for all the possible combinations of subjects (i.e., n = 126). The stability score of any hierarchy was computed by averaging the correlation coefficients across steps (i.e., n = 126).

2.5. FC gradients

We computed FC gradients using BrainSpace, a toolbox for the identification, visualization, and analysis of macroscale gradients in neuroimaging datasets (Vos de Wael et al., 2020).

The input matrix

The input matrix consisted of the voxel-wise FC between or within areas. The Pearson correlation coefficient between the time-series of every pair of voxels within and/or between areas was computed. This resulted in a 2D matrix of correlation coefficients, with every voxel being represented by an n-dimensional row vector (with n reflecting the number of connections). The connectivity matrices were computed for each subject and run.

Generating gradients

The procedure for generating FC gradients was thoroughly described in Vos de Wael et al. (2020). The input matrix was made sparse (10% sparsity) and the cosine similarity kernel was

applied to build the affinity matrix. Next, diffusion mapping was applied using the BrainSpace basic parameters.The resulting gradients were plotted on the cortical surface of the NMT template (Seidlitz et al., 2018) using AFNI (Cox, 1996) and SUMA (Ziad S Saad & Reynolds, 2012; Z. S. Saad, Reynolds, Argall, Japee, & Cox, 2004). The gradients were generated bilaterally. We only report the gradient most correlated with the INT map, assuming that ensuing gradients reflect other principles of functional organization.

Cortical projection

To probe the relationship between the striatal FC gradients and the cortex, the striatal FC gradients were projected onto the cortex according to the highest-correlated voxels (Haak et al., 2018). To reduce noise and improve interpretability, the resulting maps were smoothed using AFNI (Cox, 1996).

2.6. Projecting INTs based on FC

To examine the relationship between INTs and FC between areas (e.g., between cortex and striatum), cortical INTs were projected onto a striatal map based on cortico-striatal FC. For every striatal voxel, the top 10 highest functionally correlated cortical voxels were identified. Next, the INTs associated with these cortical voxels were extracted. Finally, the average associated cortical INT value was computed for each striatal voxel and represented as a map.

3. Results

3.1. INT hierarchies

First, we set out to replicate and validate findings from electrophysiological INT estimation with ultra-high field fMRI. Murray and colleagues (2014) initially described (in macaques) a visual cortical hierarchy of seven cortical areas: medio-temporal area (MT), lateral intraparietal (LIP) area, orbitofrontal cortex (OFC), lateral PFC (LPFC), anterior cingulate cortex (ACC); and a somatosensory hierarchy including primary somatosensory (S1) and secondary somatosensory (S2) cortex (Figure 1A-B Left). This cortical hierarchy has been replicated and further extended by assigning INTs to the dorsal premotor (PMd) cortex, frontopolar cortex (PFp), ventral and dorsal LPFC (VLPFC, DLPFC) (Cavanagh et al., 2016; Cirillo et al., 2018; Fascianelli et al., 2019) (Figure 1C-D Left). Recently, INTs have been estimated in the medial wall of the PFC, including the ventromedial PFC (vmPFC), subgenual ACC (sgACC), pregenual ACC (pgACC), and dorsal ACC (dACC) (Maisson et al., 2021) (Figure 1E Left). Lastly, a subcortical INT hierarchy has been described for regions of the basal ganglia: external segment of the globus pallidus (GPe), subthalamic nucleus (STN), and the striatum (Nougaret et al., 2021) (Figure 1F Left).

The electrophysiology-based (Figure 1 Left) and fMRI-based (Figure 1 Right) INTs reveal similar hierarchies across the brain. By replicating these physiological hierarchies, we demonstrate that fMRI is well-suited to investigate temporal aspects of whole-brain dynamics. Minor deviations from hierarchies estimated from single-unit recordings (e.g., in STN, sgACC, pgACC) can be attributed to several factors such as a high degree of INT heterogeneity within these regions, and differences between studies in the atlases used and size of the areas under investigation (see Supplementary Figures 1 and 2 for stability analysis of the INTs).

We next investigated previously unexamined regions, making unique use of our high resolution, whole brain coverage. Specifically, we reveal a hierarchy of INTs in the dorsal visual pathway (Goodale et al., 1994; Goodale & Milner, 1992) (Figure 2). INTs gradually increase from the entry point of visual information to higher order areas involved in visuo-motor integration (Figure 2, inset). INTs are hierarchically organized within the occipito-parietal, parieto-premotor and parieto-prefrontal components of the dorsal pathway (Kravitz, Saleem, Baker, & Mishkin, 2011). Also, in line with the occipito-parietal pathway being the source of the other two pathways, it is lower in the hierarchy. Taken together, we replicate electrophysiological INT hierarchies and demonstrate the invaluable contribution of using whole-brain fMRI to extend this research by describing a previously uncharacterized fine-grained temporal hierarchy along the visual pathway as an example.

3.2. INT hierarchies are closely related to FC gradients across the brain

We next examined the relationship between INTs and gradients of FC at different levels of description, starting with the frontal and parietal lobes (see Figure 3, gradients computed twice, once using within-lobe FC and again using frontal-parietal FC). In the frontal lobe, the first component (i.e., G1) shows an overall anterior-posterior organization spanning from sensory to motor areas. This aligns with previous studies showing a global anterior-posterior functional gradient in the frontal lobe (Badre, 2008; Riley, Qi, Zhou, & Constantinidis, 2018; Tan, Tang, Herikstad, Pillay, & Libedinsky, 2020). The second component (i.e., G2) shows an overall lateral-medial organization, extending from the PMv to the medial wall. The INT map was correlated with G2 for both within-area ($r = 0.47$) and fronto-parietal ($r = -0.26$) connectivity. In the parietal lobe, G1 showed a medial-lateral and G2 a ventro-dorsal overall organization. The INT map was correlated with G1 for both within-area ($r = 0.56$) and fronto-parietal ($r = -0.47$) connectivity. (Note that the sign of the gradients is arbitrary as a byproduct of the decomposition method (Haak & Beckmann, 2020), hence, only the magnitude but not the direction of the INT-FC gradient correlation is relevant.)

We then selected functionally meaningful subdivisions of the frontal lobe to probe finer-grained connectivity profiles and interrogate the existence of multiple hierarchical gradients of function (see Figure 4). In all cases, the INT maps were highly correlated with one of the principal components estimated from within-area connectivity (i.e., LPFC G1: $r = -0.35$; Motor G1: $r = -0.68$; OFC G2: $r = -0.45$; MPFC G1: $r = -0.49$). For example, the motor cortex has a well-established hierarchy, with premotor regions at the top and M1 at the bottom (Binkofski & Buxbaum, 2013; Wong, Haith, & Krakauer, 2015). Accordingly, the maps reflected this functional hierarchy, with M1 being at one end and the PMv at the other. The OFC shows a predominantly anterior-posterior axis of change, which agrees with anatomical findings—the caudal and lateral regions are more input-like unimodal regions while more anterior areas integrate these multi-modal signals (Carmichael & Price, 1994, 1996; Öngür & Price, 2000; Price, 1999). The lateral and medial subdivisions of the PFC revealed a predominately anterior-posterior organization. The same pattern of results was observed at the single-subject level (see Supplementary Figure 3).

We then investigated cortical-subcortical hierarchical gradients of function. Cortico-striatal anatomical connectivity has been extensively studied in NHPs, however, striatal-cortical FC and INTs have not. The striatal INT map was correlated with the FC gradient estimated from cortico-striatal ($r= 0.38$) connectivity (see Figure 5). The cortico-striatal FC

topography exhibited a gradual pattern of connectivity change corresponding to the anterior-posterior, dorsal-ventral, and medial-lateral anatomical gradient of connectivity derived from tract-tracing studies in NHPs (Haber et al., 2006; Friedman et al., 2002; Alexander et al., 1986; Cho et al., 2013). INTs followed a similar pattern. Moreover, the FC gradients were similar to those estimated from human neuroimaging data (Marquand, Haak, & Beckmann, 2017). To examine the underlying FC patterns, we projected the striatal gradient onto the cortex (see Figure 5A). This analysis not only validated the meaning of the gradients, but also revealed that the cortico-striatal FC closely matched anatomical connectivity. To further investigate the link between FC and INTs, we reconstructed the striatal INT map by replacing the INT of every voxel with the average INT value of the cortical voxels (i.e., 10 voxels) with which they are most correlated (see Figure 5B). In accordance with the above-mentioned results, the striatal INTs and reconstructed cortico-striatal INT maps were correlated (r= 0.45). At the voxel level, the INT values closely matched the average INTs of their top 10 strongest cortical connections.

Overall, we demonstrated that INTs are organized along spatial gradients that closely matched FC gradients.

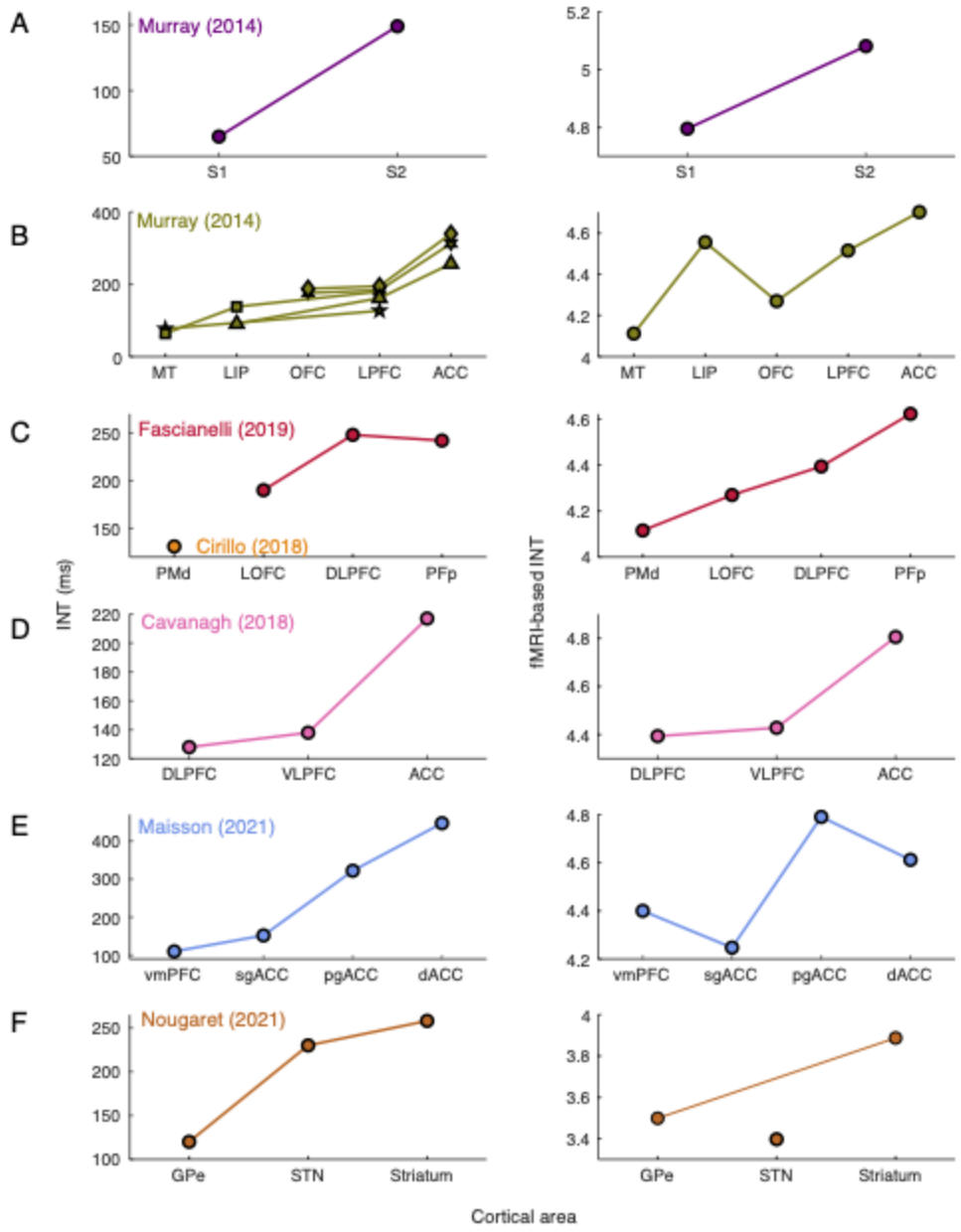

Figure 1 fMRI-based and electrophysiology-based INTs reveal a similar hierarchical ordering of cortical and subcortical areas. Each color represents an electrophysiology-based hierarchy from a different data set (Left) and its fMRI replication (Right). (A) INTs across the somatosensory hierarchy reported by Murray et al. (2014). (B) INTs across the visual hierarchy reported by Murray et al. (2014). Each symbol represents a different data set as originally reported. (C) INTs across the frontal lobe reported by Fascianelli et al. (2019) and Cirillo et al. (2018). (D) INTs across the PFC reported by Cavanagh et al. (2018). (E) INTs across the MPFC reported by

Maisson et al. (2021). (F) INTs across the basal ganglia reported by Nougaret et al. (2021). The cortical areas were defined separately for each panel to match the recording sites of the data set. Abbreviations: S1/S2 (primary/secondary somatosensory cortex), MT (middle temporal area), LIP (lateral intraparietal area), OFC (orbitofrontal cortex), LPFC (lateral prefrontal cortex), ACC (anterior cingulate cortex), PMd (dorsal premotor cortex), LOFC (lateral OFC), DLPFC (dorso-lateral PFC), VLPFC (ventro-lateral PFC), PFp (polar prefrontal cortex), vmPFC (ventro-medial PFC), sgACC (subgenual ACC), pgACC (pregenual ACC), dACC (dorsal ACC), GPe (external globus pallidus), STN (subthalamic nucleus).

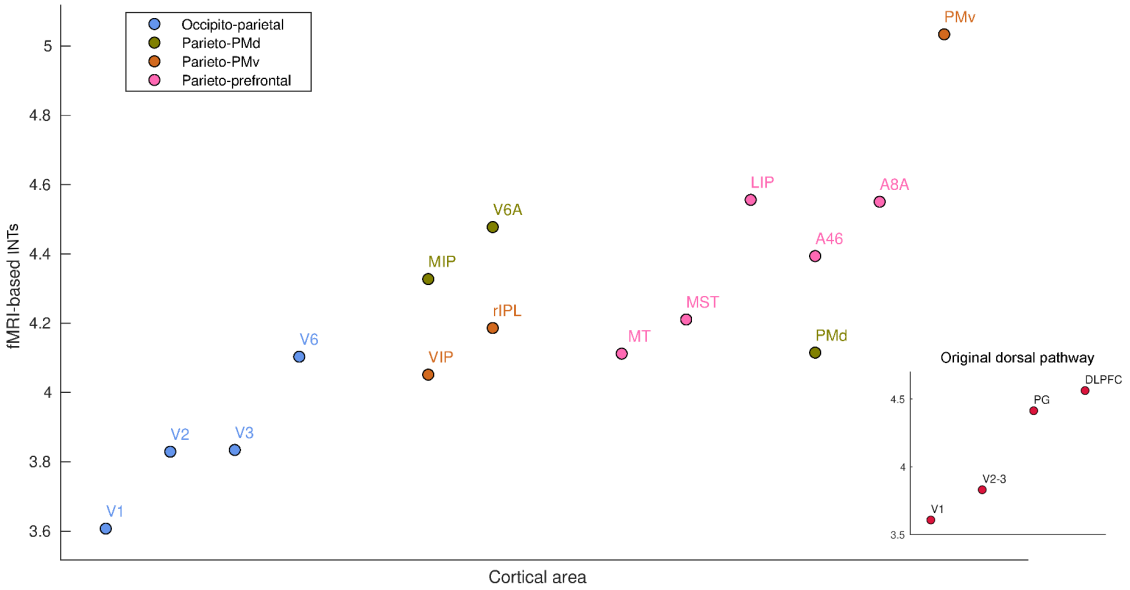

Figure 2 fMRI reveals a hierarchical ordering of INTs in the dorsal pathway for visuospatial processing. The dorsal pathway reveals a gradual progression of INTs from sensory to association and motor cortices. The hierarchical pattern of INTs can be observed in the original description of the dorsal pathway (inset), but also in more recently described subdivisions. Every color represents a subdivision of the dorsal pathway as described in Kravitz, Saleem, Baker, & Mishkin (2011). The ROIs were defined bilaterally based on CHARM (see Supplementary Table 2). Abbreviations: DLPFC (dorso-lateral prefrontal cortex), VIP (ventral intraparietal area), MIP (medial intraparietal area), rIPL (rostral inferior parietal lobule, MT (middle temporal area), MST (medial superior temporal area), LIP (lateral intraparietal area), A46 (area 46), A8A (area 8A), PMd (dorsal premotor cortex), PMv (ventral premotor cortex).

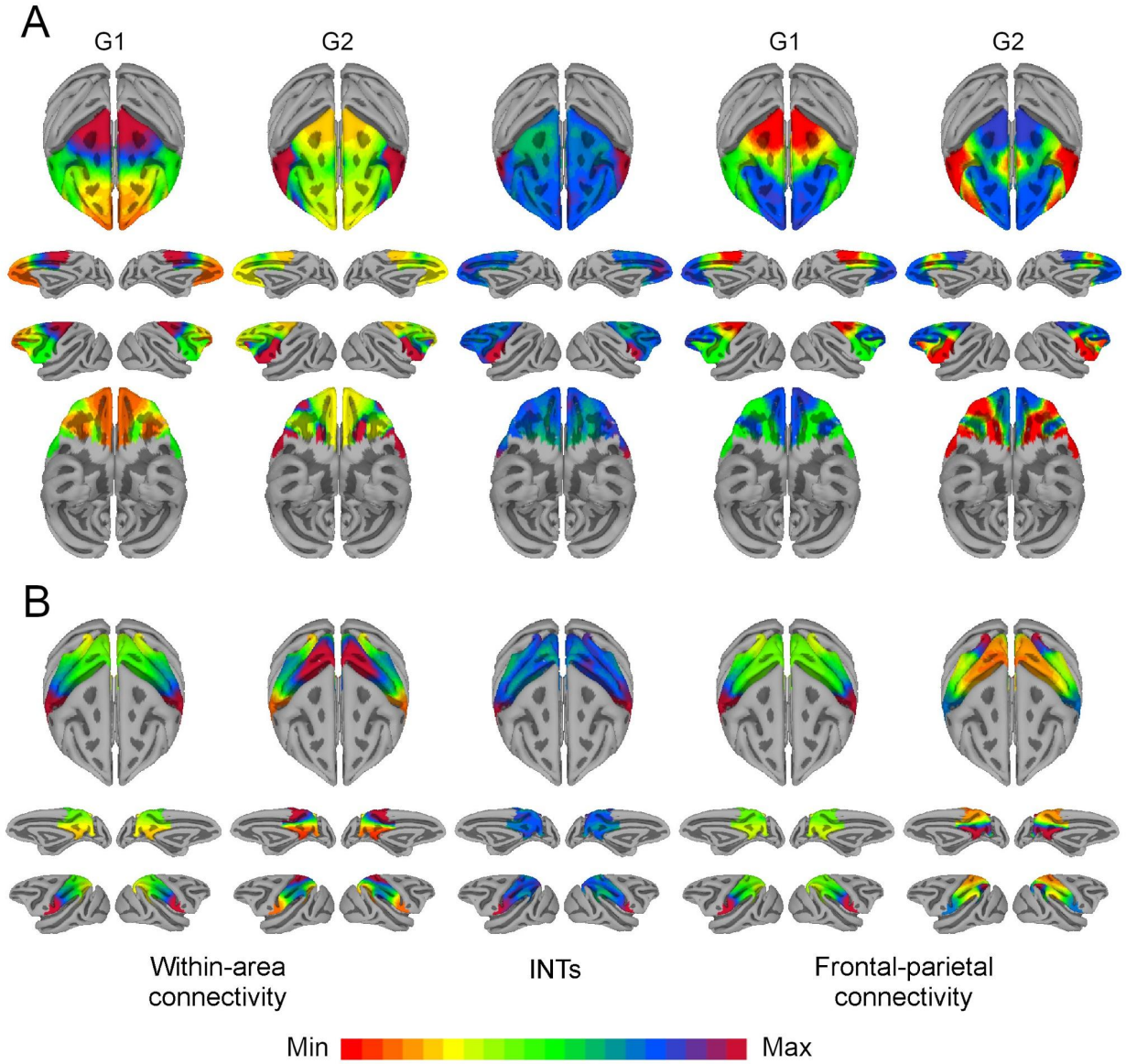

Figure 3 Cortical FC gradients are related to INTs. The first two gradients were estimated based on within-area connectivity (Left) and frontal-parietal connectivity (Right). INTs are presented as a comparison (Middle). (A) Frontal INTs are correlated with G2 for both within-area and frontal-parietal connectivity. (B) Parietal INTs were correlated with G1 for both within-area and parietal-frontal connectivity. The color bar indicates the position along the dominant mode of connectivity change (values are on an arbitrary scale) or INT values (higher values indicate slower timescales). The maps were computed at the group level (N = 9). The value ranges differ across panels unless otherwise stated. Abbreviations: G1 (Gradient 1), G2 (Gradient 2).

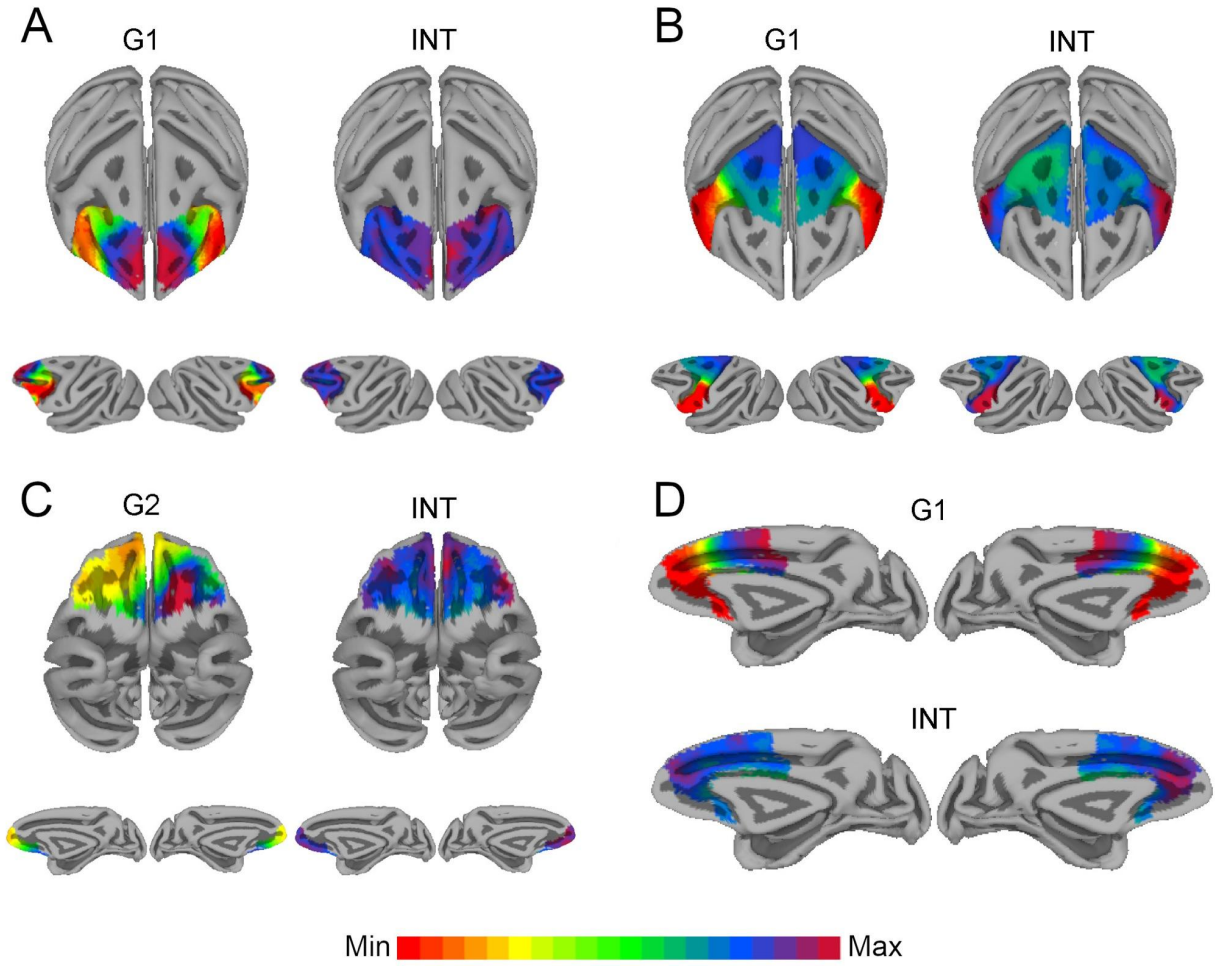

Figure 4 The relationship between FC and INTs in the frontal cortex. The INT map (Right) and corresponding within-area gradient (Left) (i.e., the gradient with the highest correlation to INTs) are presented. (A) INTs in the LPFC were correlated with G1. (B) INTs in the motor cortex were correlated with G1 (C) INTs in the OFC were correlated with G2 (D) INTs in MPFC were correlated with G1. The color bar indicates the position along the dominant mode of connectivity change (values are on an arbitrary scale) or INT values (i.e., higher values indicate slower timescales). The value ranges differ across panels unless otherwise stated. The maps were computed at the group level (N = 9). Abbreviations: G1 (Gradient 1), G2 (Gradient 2).

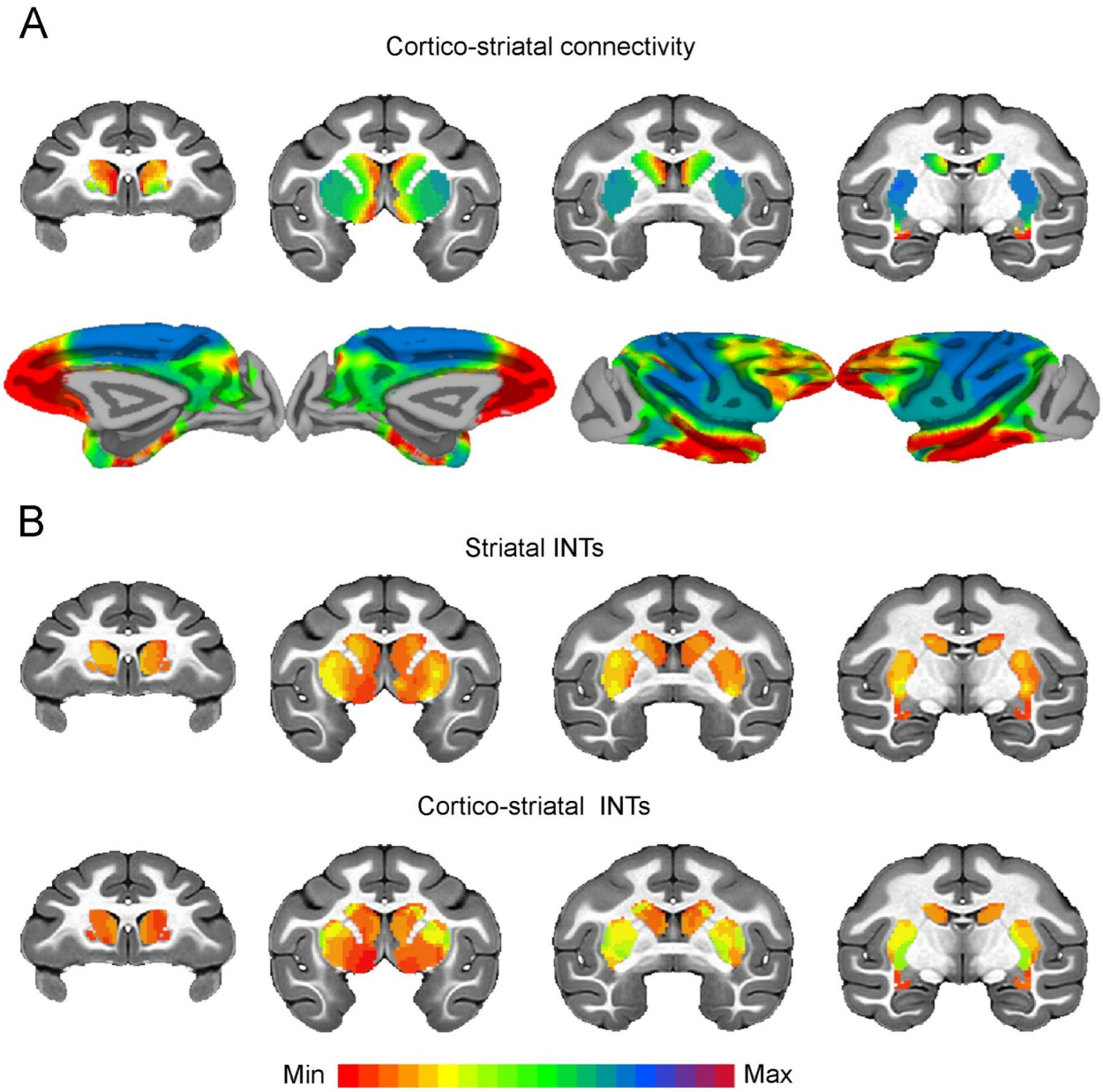

Figure 5 Cortico-striatal FC is related to INTs. (A) The striatal FC gradient estimated from cortico-striatal connectivity (Top) and its projection onto the cortex (Bottom) (Note: the same value range was used). The FC patterns underlying the cortico-striatal gradient matched the anatomical connectivity derived from animal invasive tracing. (B) Striatal INTs (Top) and cortical INTs projection based on cortico-striatal FC (Bottom). The striatal and cortico-striatal INT maps were related. Striatal INTs were related to G1 estimated from cortico-striatal connectivity.The color bar indicates the position along the dominant mode of connectivity change (values are on

an arbitrary scale) or INT values (higher values indicate slower INTs). The value range differs across panels unless otherwise stated. The maps were computed at the group level (N = 9).

4. Discussion

Temporal integration is a fundamental property of neural processing (Cavanagh, Hunt & Kennerley, 2020; Hasson et al., 2008; Honey et al., 2012; Soltani et al., 2021), both during task performance and in the absence of external stimulation (Cirillo et al., 2018; Hasson et al., 2008; Murray et al., 2014; Raut et al., 2020). However, there have, until this point, been major gaps in investigating temporal integration across the brain, across species, and across populations. This is because, traditionally, temporal integration has been studied primarily using single-unit electrophysiology in NHPs (although see Gao, van den Brink, Pfeffer, & Voytek, 2020). Although there is some evidence that BOLD signals from fMRI may allow for whole brain interrogation of timescales in humans (Watanabe et al., 2019; Wengler et al., 2020), such an approach had not yet been validated. Here, we focused on investigating whole-brain INT and FC topographies at different levels of description, to first validate, within-species, the study of INTs using BOLD fMRI, and then investigate the relationship between temporal and spatial dynamics of the resting brain with ultra-high resolution fMRI across the whole macaque brain.

We have demonstrated the feasibility of estimating INTs from fMRI in the NHP brain. We did so by showing that hemodynamic INT hierarchies closely match those derived from NHP electrophysiology. While some recent human neuroimaging studies have investigated whole-brain hemodynamic INTs (Raut et al., 2020; Watanabe et al., 2019; Wengler et al., 2020), temporal hierarchies derived from electrophysiology have not been replicated via fMRI, nor within species. Furthermore, in a previous paper, INTs derived from fMRI data in human subjects were elegantly validated with EEG (Watanabe et al., 2019). The present findings are in agreement with these results, finding slower and shorter INTs in frontoparietal areas and sensory-related areas, respectively. This points towards cross-species homologies in cortical INTs, hence laying the groundwork for future translational work. Nevertheless, the step presented here is essential, because we were able to validate fMRI estimates of INTs with single neuron spiking results within-species. This finding provides validation for the complementary use of hemodynamic and electrophysiological INTs. Using fMRI in this context has several advantages. First, it can be performed on the whole brain. Second, it can easily be employed across different human populations in the future, dramatically expanding the possible uses of INT investigations.

We did observe minor deviations from electrophysiological INTs in our data. These may be in large part attributable to a high degree of INT heterogeneity within individual anatomical regions. This observation is in line with previous reports of heterogeneity within neural populations in single-unit recordings (Cirillo et al., 2018; Nougaret et al., 2021). This suggests that averaging INTs within anatomical regions might not provide a full description of macroscale organization.

To further demonstrate the potential of INTs estimated from fMRI, we extend the current literature by providing a finer description of visual hierarchy INTs than previously described electrophysiologically (Murray et al., 2014). Remarkably, areas along the dorsal visual pathway follow the INT hierarchical ordering predicted by functional specialization and connectivity (Kravitz et al., 2011), with primary visual areas showing the fastest timescales and prefrontal

areas showing the longest. Our findings bring further evidence that the dorsal pathway is not a unitary system, but rather subdivided into multiple parallel pathways (Binkofski & Buxbaum, 2013; Kravitz et al., 2011). This demonstrates the importance of fine-grained, large-scale descriptions of the brain for uncovering multiple hierarchies.

We investigated timescales and connectivity topographies at different levels of description to probe whether one aspect of the multi-dimensional functional architecture of the brain is related to temporal structure. We show that INT topographies are closely related to the overlapping FC gradient dimensions. Previous studies have demonstrated that FC gradient dimensions in sensory cortex corresponded with known organizational principles such as eccentricity and polar angle (Haak et al., 2018). Moreover, FC gradients followed M1's somatotopic map. Our findings put forward a significantly more unified framework that generalizes over the entire brain. INTs form a topographic organizational principle ranging from sensory to associative cortex. While other organizational principles can and likely always will be represented across topographic networks of the brain, intrinsic timescales appear to be special in their general extent.

INTs, like anatomical connectivity and FC, are one way of characterizing the organization of the brain. Critically, combined maps of all three will require a nonhuman animal model such as the macaque, as anatomical connectivity cannot be directly measured in humans (Grier, Zimmermann & Heilbronner, 2020). It is clear that anatomical connectivity, FC, and INTs are related, although the precise nature of the relationships is somewhat speculative. For instance, vertex FC strength is related to human INTs estimated from fMRI (Raut et al., 2020). Our own results show that cortico-striatal INTs and FC gradients broadly track anatomical connectivity. Anatomical connectivity establishes the pathways which the signals underpinning FC use. However, the fact that the pathways exist and are used does not tell us what types of information transformations occur along the way. Through cascaded processing, longer and longer TRWs can be built, measured as longer INTs. Thus, we expect that the space of potential INTs is constrained by both anatomical and functional connectivity. Future exploration of these organizational principles, including using pharmacological interventions and electrical stimulation, will likely clarify the causal relationships at play.

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