

Mapping of Motor Sequence Representations in the Human Brain across learning and consolidation

Basile Pinsard ^{*1,2}, Arnaud Boutin ¹, Ella Gabitov ¹, Habib Benali ^{1,2}, and Julien Doyon ¹

¹ Functional Neuroimaging Unit, Centre de Recherche de l’Institut Universitaire de Gériatrie de Montréal, Montreal, Quebec, Canada

² Sorbonne Universités, UPMC Univ Paris 06, CNRS, INSERM, Laboratoire d’Imagerie Biomédicale (LIB), 75013, Paris, France

June 30, 2016

Introduction

The capacity to acquire novel sequences of movements have shown to contribute critically to the complex evolving repertoire of motor actions in animals and humans. Motor sequence learning (MSL), defined as the acquisition of temporally ordered succession of coordinated movements, has thus often been employed to study the behavioral determinants of this type of procedural memory.

While practice of MSL over several training sessions lead to substantial improvement in performance, evidence of further offline reprocessing of the acquired procedural memory have accumulated (Walker et al. 2003; Press et al. 2005; Hotermans et al. 2006; Korman et al. 2007; Morin et al. 2008; Debas et al. 2010; Barakat et al. 2013; Cousins et al. 2014; Debas et al. 2014; Gregory et al. 2014; Cellini and McDevitt 2015; Ramanathan, Gulati, and Ganguly 2015; Laventure et al. 2016). This reprocessing is observed as either gains or maintenance of performance compared to a decay if no offline period is allowed to the subject (Nettersheim et al. 2015). Explicitly acquired sequential skills specifically benefit from this off-line reprocessing (Doyon et al. 2009). However controversies remains regarding the respective roles that both wake and sleep stages play in consolidating motor memory traces (Nettersheim et al. 2015; Landry, Anderson, and Conduit 2016).

Sequential motor skills recruit an extended network of cerebral (Hardwick et al. 2013), cerebellar and spinal regions (Vahdat et al. 2015), which involvement evolves differently across learning stages (Dayan and Cohen 2011). Herein, critical plasticity changes (Ungerleider, Doyon, and Karni 2002; Doyon and Benali 2005) occurs at both training and consolidation, the latter being modelled (Rasch and Born 2008; Born and Wilhelm 2012; Albouy, King, et al. 2013; Dudai, Karni, and Born 2015) as a “transfer” or “reorganization” between cerebral structures supporting the function.

Both cortico-cerebellar and cortico-striatal loop circuits contributes to MSL (Doyon and Benali 2005), recruiting primary sensorimotor and supplementary motor cortices as well as posterior parietal and dorso-lateral prefrontal cortices (Hardwick et al. 2013) concurrently to sub-parts of cerebellum and striatum on which we will further expand.

Cerebellar cortex anatomical functions (Diedrichsen and Bastian 2014) include integration of sensory and motor ipsilateral finger representation in Lobule V (Wiestler, McGonigle, and Diedrichsen 2011), complex movements, including coordination, sequencing and spatial processing, which recruit the bilateral Lobule VI (Schlerf et al. 2010) and Crus I in Lobule VII (Doyon et al. 2009), being respectively connected to primary and premotor and supplementary cerebral cortices (Buckner et al. 2011). Lobule VIII also shows a somatotopically organized representation of the whole body, but weaker relatively to Lobule V/VI. Cerebellar contributes to model-based prediction and sensory feedback processing (Tseng et al. 2007), thus support error-based learning in early MSL. This is observed by an activation shift from cerebellar cortex to dentate nuclei (Doyon et al. 2002) and lowered activation with extended practice, orthogonal to striatal-cortical loop increased recruitment.

The striatum has been associated in selection, preparation and execution of free or instructed movements (Hikosaka et al. 2002; Gerardin et al. 2004; Doyon et al. 2009), as well as automation of sequences processing through reinforcement learning (Jin, Tecuapetla, and Costa 2014), the caudate nuclei activity increasing with decreased execution variability (Albouy et al. 2012). The striatum, and more specifically the putamen, was revealed to be implicated in the consolidation of the motor memory trace (Debas et al. 2010; Albouy, King, et al. 2013; Debas et al. 2014). With extended training over multiple weeks, a

*basile.pinsard@gmail.com

progressive shift from associative and premotor to sensorimotor basal ganglia distributed network concurs to the automation of the skill (Lehéricy et al. 2005).

Hippocampus is a major structure for memory (Battaglia et al. 2011) that not only encodes episodic memories, including spatial and sequenced events (Howard and Eichenbaum 2015; Moser, Rowland, and Moser 2015), but also supports procedural memory acquisition in its early stages (Albouy et al. 2008), its activity and interaction with striatum predicting sequences long-term retention (Albouy, Sterpenich, et al. 2013). This hippocampal procedural representation could concurrently bind episodic memory of task execution, an allocentric representation (Albouy et al. 2015) and temporary tagging and buffering of memories to be further consolidated.

The abovementioned structures undergo non-linear changes of activation level during the course of learning (Dayan and Cohen 2011), notably after consolidation (Lehéricy et al. 2005; Debas et al. 2010; Debas et al. 2014), reflecting both increased implication of specialized circuits and decreased non-specific support networks activation.

While these large-scale activation changes excerpt the dynamics of the recruited networks, it does not provide evidence that these are directly involved in acquiring motor sequence specific representation. This can, however, be identified with Multivariate Pattern Analysis (MVPA), a set of techniques recently adapted to neuroimaging (Pereira, Mitchell, and Botvinick 2009), which evaluates how local patterns of activity are able to discriminate between stimuli or memories of the same class.

To our knowledge, few studies have applied MVPA to MSL, with various design aimed at specific identification of whole sequence or features representation.

In a recent study focusing on motor-related cerebral cortices (Wiestler and Diedrichsen 2013), classifier performance was evaluated on sets of sequences (either trained or not) and showed a potential increase of the representation strength with training in a 1network spanning bilaterally the primary motor, pre-motor and supplementary motor areas to the parietal cortex. The different sequences were interleavedly trained over 4 days with immediate feedback, ensuring stable execution and representation of the sequence, while averaging over multiple executions allowed more stable patterns. Analyzing the dynamics of classifier decoding performance they also uncovered the timecourse of motor sequence representation in different cortical areas from instruction to execution, slightly preceding the BOLD response.

Prior to motor sequence execution, preparation activates a network that overlaps with the one activated during movements per se (Lee, Chang, and Roh 1999; Zang et al. 2003; Orban et al. 2015), thus, another study (Nambu et al. 2015) specifically analyzed patterns of activity after instruction and prior to execution of extensively trained sequences with dominant hand. Patterns related to motor planning without contamination of motor execution or sensory feedback related activity were detected in a restricted network involving the contralateral dorsal premotor and supplementary motor area, but not the basal ganglia.

Using high-resolution imaging and averaging multiple trials, another study (Bednarik, Campbell, and Cunnington 2015) found activation differences in the striatum between rhythmic and ordered motor sequences executions, whereas MVPA failed to find discriminating patterns. Yet, the latter pattern of negative findings using MVPA could be due to the fact that sequences were not trained and that the authors used cross-conditions (rhythmic vs. order) classification of averaged trials thus lowering patterns specificity.

Numerous neuroimaging (Hikosaka et al. 2002; Albouy et al. 2008; Orban et al. 2010; Penhune and Steele 2012; Albouy et al. 2012) and neuronal level studies (Alexander, DeLong, and Strick 1986; Graybiel 1995; Miyachi, Hikosaka, and Lu 2002) have corroborated the implication of basal ganglia, notably the striatum, as well as hippocampus, in acquisition and consolidation of sequential motor skills.

Nevertheless, the acquisition of motor sequence representation during MSL in these regions critical to MSL is still to be assessed.

The goal of the present study is thus to identify acquisition of finger presses sequences representation and their reorganization during consolidation in structures critical to MSL including striatum, hippocampus and cerebellum, by combining MVPA and robust statistics to assess decoding significance (Stelzer, Chen, and Turner 2013; Allefeld, Görgen, and Haynes 2015).

The dynamic of sequential movement planning to execution will also be decomposed to separately analyze instruction and execution phases for that they should show different while overlapping representation (Wiestler and Diedrichsen 2013; Nambu et al. 2015).

Learning and sleep-dependent changes will be assessed by comparing MVPA results for sequences while being acquired, after acquisition and after consolidation.

We hypothesize that cortical, striatal and hippocampal sequence representation acquisition follows different time course during MSL (Albouy, Sterpenich, et al. 2013), and consolidation induces a significant network reorganization (Debas et al. 2014).

Method

Participants

The study includes ## right-handed young (18-35 years old) healthy volunteers recruited by advertising on scholar and public website.

The subject were not included in case of history of neurological psychological or psychiatric disorders or scoring 4 and above on the short version of Beck Depression Scale (Beck et al. 1961).

Subjects with BMI greater than 27, smokers, extreme chronotype, night-workers, having travelled across meridian during the 3 previous months, or training as musician or professional typist (for over-training on coordinated finger movements) were also excluded.

Sleep quality was assessed by Pittsburgh Sleep Quality Index questionnaire (Buysse et al. 1989), and daytime sleepiness (Epworth Sleepiness Scale (Johns 1991)) had to be lower or equal to 9.

Subject were also instructed to abstain from caffeine, alcohol and nicotine, and have regular sleep schedule (bed-time 10PM-1AM, wake-time 7AM-10AM) and avoid taking daytime nap for the duration of the study. Instruction compliance was controlled by non-dominant hand wrist actigraphy (Actiwatch 2, Philips Respironics, Andover, MA, USA) for the week preceding and the duration of the experiment.

Behavioral experiment

The experiment was conducted over 3 consecutive days, at the end of the day, with all motor task performed in the scanner using an ergonomic MRI-compatible 4-keys response pad.

First evening (D1)

Subjects were trained to perform with left-hand a 5 elements sequence (TSeq) for 14 blocks of 12 sequences or a maximum of $12 \times 5 = 60$ keypresses. Subject were instructed to execute repeatedly as fast and as accurate as possible the sequence of keypresses and to start from the beginning of the sequences in case they noticed that they did an error.

They were retested approximately 20 minutes later for an additional single block of 12 sequences.

Second evening (D2)

Subjects were first tested for 1 block on TSeq, then half of the subjects of “Interference” (Int) group were trained on an interfering sequences (IntSeq) of 5 elements with left-hand for 14 blocks of 12 sequences as for TSeq. “No-Interference” (NoInt) group had scanned resting-state which duration was yoked to a IntGroup subject.

Third evening (D3)

Subjects first performed TSeq for 7 blocks of 12 repetitions for retest, then practised IntSeq for 7 blocks of 12 sequences.

This was followed by a task specifically designed for MVPA analysis, that will be called “MVPA task” thereafter. This task was similar to (Wiestler and Diedrichsen 2013), rapidly alternating short blocks of practice of 4 different sequences.

Significant differences are that 4 sequences were performed with the left hand four fingers excluding the thumb and no feedback was given regarding the correctness of performance. Also sequences were repeated uninterruptedly as in training, in order to probe the processes underlying automation of the skill.

Each block, composed of an instruction period of 4 sec when was displayed 5 numbers (eg. 1-4-2-3-1) representing in reading order the sequence of fingers to be pressed, followed by an execution period indicated by a green cross. Subject had to perform 5 times the sequence, or a maximum of $5 \times 5 = 25$ key-presses before being instructed to stop and rest by displaying a red cross.

Rest duration was variable and set to synchronize the beginning of each block with the same slice in the volume being acquired to allow study of dynamics as further described.

Ordering of the sequences in blocks was chosen to include all possible successive pairs of the sequences using De Bruijn cycles (Aguirre, Mattar, and Magis-Weinberg 2011) allowing unbiased analysis of dynamics described below. Given 4 sequences, a 2-length De Bruijn cycle would contains 16 blocks, repeated twice to give 8 repetitions of each of the 4 sequences which amounts to 32 blocks.

Each subject performed the task twice in scans separated by few minutes to allow rest and enable study of cross-scans pattern stability using classification generalization.

Scan acquisition

MRI data were acquired on a Siemens Trio 3T scanner on 2 two separate sessions. The first session used 32-channel coil to acquire high-resolution anatomical T1 weighted image using Multi-Echo (4) MPRAGE (MEMPRAGE) at 1mm isotropic resolution.

Functional data were acquired during the second session with 12-channel coil for comparison with other dataset. EPI sequence consists of 40 slices with 3.44mm in-plane resolution and 3.3mm slice thickness to provide full cortical and cerebellum coverage with a TR of 2.16 sec. Consecutively fieldmap was obtained to measure B0 field inhomogeneity to allow retrospective compensation of induced distortions.

Preprocessing

Custom pipeline was used to preprocess fMRI data prior to analysis. First, high-resolution anatomical T1 weighted image was preprocessed with Freesurfer (Dale, Fischl, and Sereno 1999; Fischl et al. 1999; Fischl et al. 2008) to segment subcortical regions, reconstruct cortical surfaces and provide inter-subjects alignment of cortical folding patterns. Pial and grey/white matter interface surfaces were downsampled to match the 32k sampling of Human Connectome Project (HCP) (Glasser et al. 2013) and we averaged pial and white surface to get coordinates at the half of the thickness of cortical sheet. HCP subcortical rois coordinates were warped onto individual T1 data using non-linear registration based on Ants software (Avants et al. 2008; Klein et al. 2009). Combination of cortical and subcortical coordinates then corresponds to grayordinates of HCP datasets (Glasser et al. 2013).

fMRI data underwent estimation of subject motion (Roche 2011) and coregistration to T1. Registration and motion parameters were used to interpolate Blood-Oxygen-Level-Dependent (BOLD) signal at anatomical grayordinates above-mentioned taking into account B0 inhomogeneity induced distortions using fieldmap acquisition.

BOLD signal was further processed to remove drifts and motion-related abrupt signal change.

Of note is that our preprocessing does not include smoothing, even though interpolation inherent to any motion correction causes averaging of values of neighboring voxels. We intended to minimize blurring of data to preserve fine-grained patterns of activity, resolution of relevant patterns being hypothetically at columnar scale.

Multivariate Pattern Analysis

Similarly to (Wiestler and Diedrichsen 2013; Nambu et al. 2015) we aim to uncover activity patterns predicting the sequence prepared or executed. We also aim to analyze the classification of trained sequences versus untrained one, however TSeq and IntSeq are probably still undergoing consolidation by the third day of the study, potentially lowering their pattern stability.

For this reason, we first aimed at classifying untrained sequences which are comparable as being completely new to the subjects, and are learned along the course of the “MVPA task”. This 2-class scheme allows mapping representation of non-consolidated sequence.

Then TSeq and IntSeq are also analyzed separately in IntGroup mapping sequences consolidated on two separate nights of sleep.

Moreover, the instruction stimuli presented before each execution, enable disambiguation of the memory traces from explicit recall from that during execution of the motor plan.

The MVPA analysis was based on PyMVPA software (Hanke et al. 2009) package with additional development of custom cross-validation scheme, Searchlight and measures to adapt to the study design and analyses.

Samples

Each block was modeled by having 2 boxcars, respectively instruction and execution phase, convolved with Hemodynamic Response Functions (HRF). Volumes (TRs) corresponding to HRF level above 50% of maximum response level were taken as samples for the performed sequence. Maximum value of instruction and execution regressors determine the TR to pertain to instruction or execution phase, for which HRF is overlapping. A TR based approach was chosen to explore the fine dynamic of patterns related to the task, that model driven such as GLM cannot fully analyze at the cost of lower signal-to-noise ratio.

Regular GLM-based approach was also performed using least-square separate (LS-S) regression of each event (Mumford et al. 2012) shown to provide improved activation patterns estimates for MVPA. For each blocks, regressors for instruction and execution phases provided t-value maps that was further used as MVPA samples.

Cross-validation

The De Bruijn cycles ordering of the sequence in the task aims at providing unbiased cross-validation by balancing the temporal succession of any pair of the 4 sequences.

Chosen cross-validation schema includes:

- Leave-One-Chunk-Out (LOCO): each block is successively taken out of the dataset to be used in prediction. Classifier is trained on remaining data by randomly selecting balanced number of samples of the 4 sequences which are further than 60 seconds to the block of test data. Random selection of balanced data is performed 5 times for each of the 64 blocks amounting to $64*5 = 320$ folds of cross-validation. When applied for each scans separately, each contained 32 blocks generating 160 fold cross-validation.
- Leave-One-Scan-Out (LOSO): random balanced subset of samples from a scan is fed for training to the classifier which then predicts one the other scan the sequences. A random balanced subsets was selected 5 times for the 2 scans giving 10 cross-validation folds.

Searchlight analysis

Searchlight (Kriegeskorte, Goebel, and Bandettini 2006) is an exploratory technique that apply MVPA techniques repeatedly on small spatial neighborhood with the purpose to localize representation of information of interest across brain while avoiding high-dimensional limitation of multivariate algorithms.

Applying cross-validation using the Searchlight schema allowed to extract brain-wise map of classifier performance giving information of regions having stable sequences related patterns. Gaussian Naive Bayes (GNB) linear classifier, optimized for Searchlight, was performed with the 2 proposed cross-validation schema analysis on the execution labelled TRs. Also GNB-based Searchlight have been argued to allow smoothness of generated maps (Raizada and Lee 2013) despite unsmoothed data, allowing more-reliable cross-subject study and thus higher cross-scans generalization.

Searchlight was configured to select for each grayordinate the 64 closest neighboring coordinates, using surface distance for cortical grayordinates, as the subset of features. Searchlight size has been shown to inflate the extent of significant clusters in searchlight analysis (Viswanathan, Cieslak, and Grafton 2012; Etzel, Zacks, and Braver 2013) which motivated the small neighborhood for our analysis.

For both cross-validation schema, confusion matrix was computed for each block of practice providing a more complete representation of classification performance and biases from which can be derived specific or global accuracy percentage.

Searchlight Group Analysis

In order to obtain the cluster with significant prediction at the group level, we used non-parametric permutation based statistical approach as described in (Stelzer, Chen, and Turner 2013). Subject-level searchlight accuracy map were computed 100 times after permuting the labels, giving a null distribution of classification accuracy per spatial coordinate. A non-parametric null distribution of mean group accuracy map was obtained by repeating 10000 averages of randomly picked subject-level permuted maps to create a featurewise threshold map at $p < 0.001$. Above threshold group permutation maps clusters were used to estimate a null distribution of cluster size enabling computation of clusters significance in the non-permuted thresholded map.

This permutation procedure was conducted for each type of searchlight.

Dynamics analysis

Also we complemented the analysis by taking TRs subsamples with similar delay from instruction time, ranging from -2 to 20 TRs, and then to discriminate the sequences in cross-validation schema. Having 64 blocks in total across the 2 scans give 64 samples for each TR delay. This is similar to (Wiestler and Diedrichsen 2013, fig. 4, D-E) ROI based temporal analysis.

Such analysis aims at uncovering the dynamics of motor sequence execution, as instruction phase might causes motor planning and simulation of sequence performance, while execution phase generally includes warm-up and then automation of motor chunks execution. Furthermore, this method is independent of HRF model allowing potential non-hemodynamic related neurally-driven BOLD signal changes to be taken into account.

While the rapid block design might hamper temporal disambiguation, De Bruijn cycle ordering imposes balanced successive blocks pairs in the dataset. Thus temporal leaking of BOLD activity of the previous sequence production is then balanced across the 4 sequences and should yield chance level prediction if no signal related to the present sequence is observable in the data, allowing unbiased analysis relative to the chance level.

Region of Interest (ROI) analyzes

A network of local neuronal populations has been shown to contribute to sequence production learning (Dayan and Cohen 2011), with their activity (Albouy, King, et al. 2013; Barakat et al. 2013) evolving in accordance theoretical models of consolidation (Born and Wilhelm 2012). To extract whether their activity independently encodes the spatio-temporal pattern of the sequence, we conducted ROI cross-validation using a priori atlas including:

- hippocampus, cerebellum and striatum including caudate nucleus and putamen
- cortical network including posterior parietal, primary motor, premotor, supplementary motor area and dorso-lateral prefrontal.

To assess the significance of each of these cross-validation accuracy measures, non-parametric permutation test (Stelzer, Chen, and Turner 2013) of xxx repetitions was conducted for each subject and ROI to estimate chance level distribution of accuracy.

Results

Searchlight

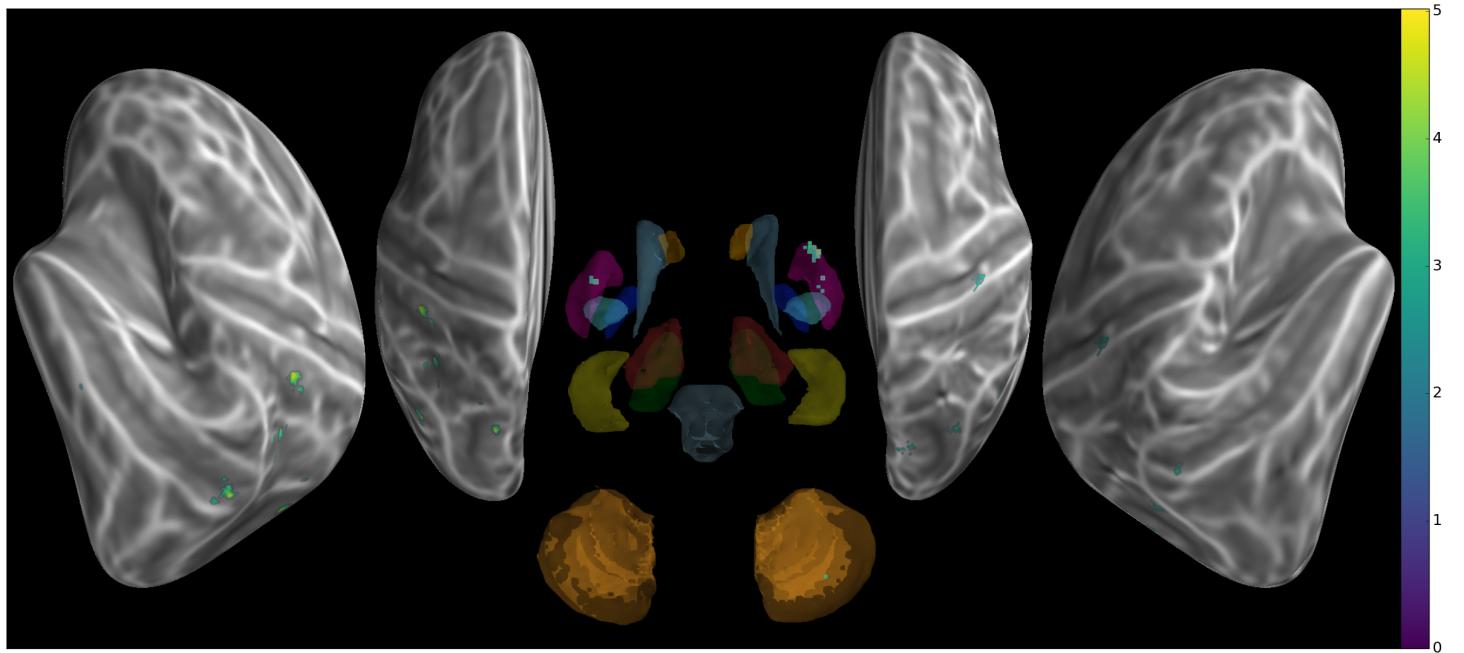


Figure 1: All subjects t-values threshold ($p < .01$) of untrained sequences classification accuracy during execution

Non-consolidated additional sequences were analyzed separately to provide a localizer of early sequence representation (fig. 1). A limited network emerges from both instruction and execution phase patterns, left hippocampus and primary motor and posterior parietal cortex, bilateral cerebellum, anterior putamen and insular cortex. This weaker representation of new sequence is in agreement with (Wiestler and Diedrichsen 2013) but could be sourced in higher variability in motor production for a part.

Consolidated sequences in Int group has, despite lower number of subjects, an extended representation spanning over posterior parietal and premotor cortex, cerebellum, caudate and putamen bilaterally (fig 3). When contrasted with the untrained sequences (fig 4), only bilateral anterior putamen clusters contains significantly higher discrimination patterns relative to untrained sequences.

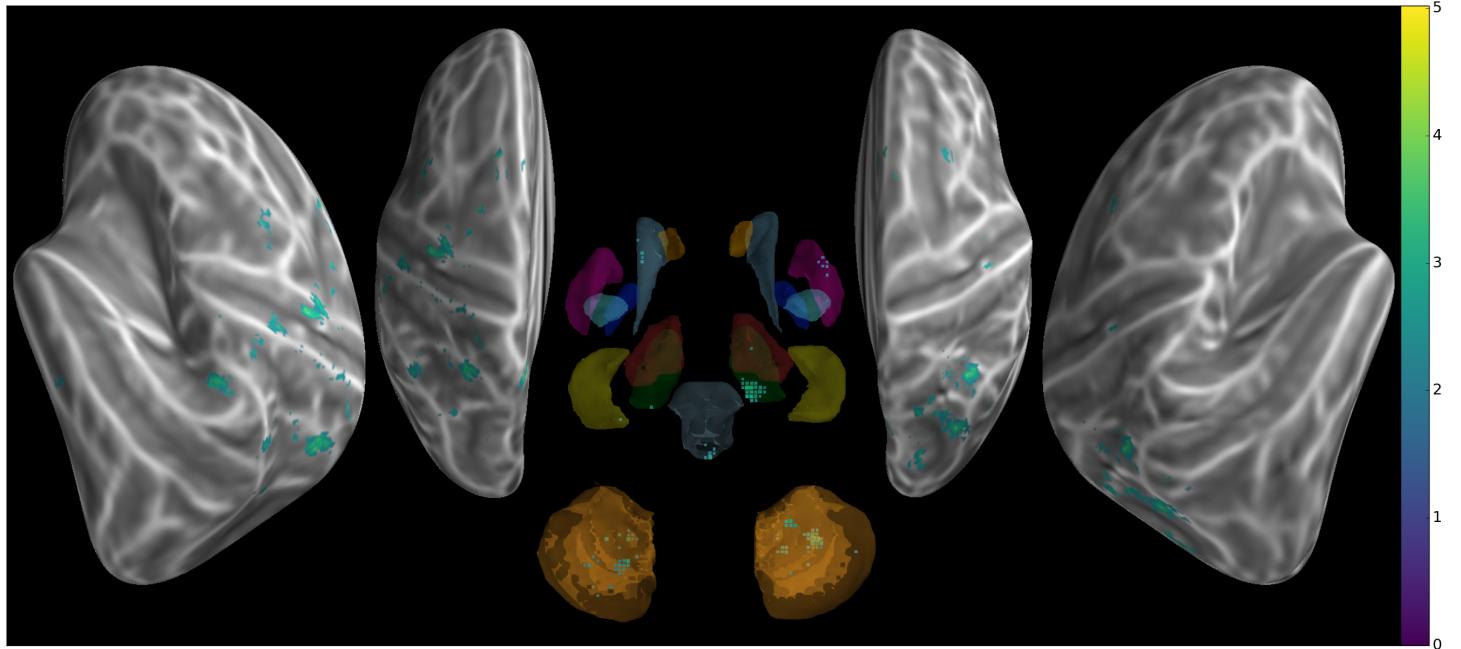


Figure 2: Contrast conjunction (scan2-scan1, scan2>chance) for untrained sequences classifier accuracy during execution t-values ($p<0.05$)

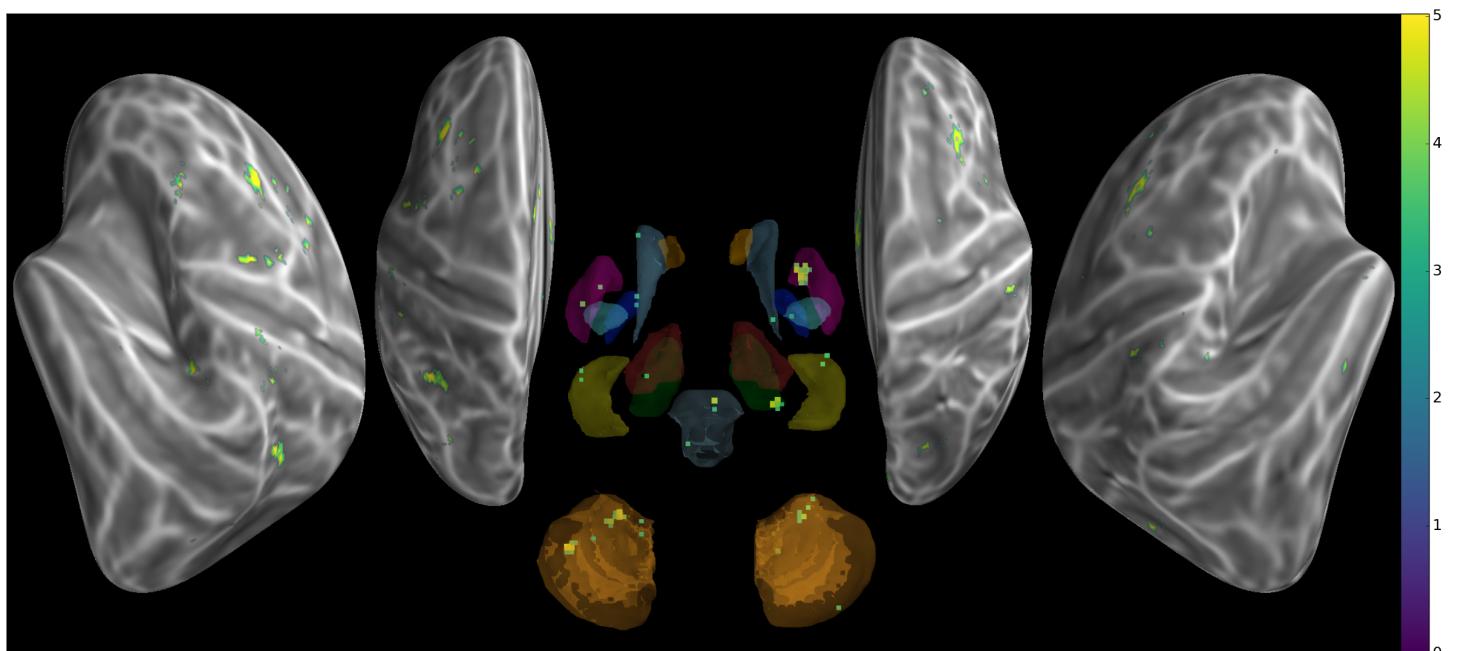


Figure 3: Int Group t-values threshold ($p<.01$) of trained sequences classification accuracy during execution

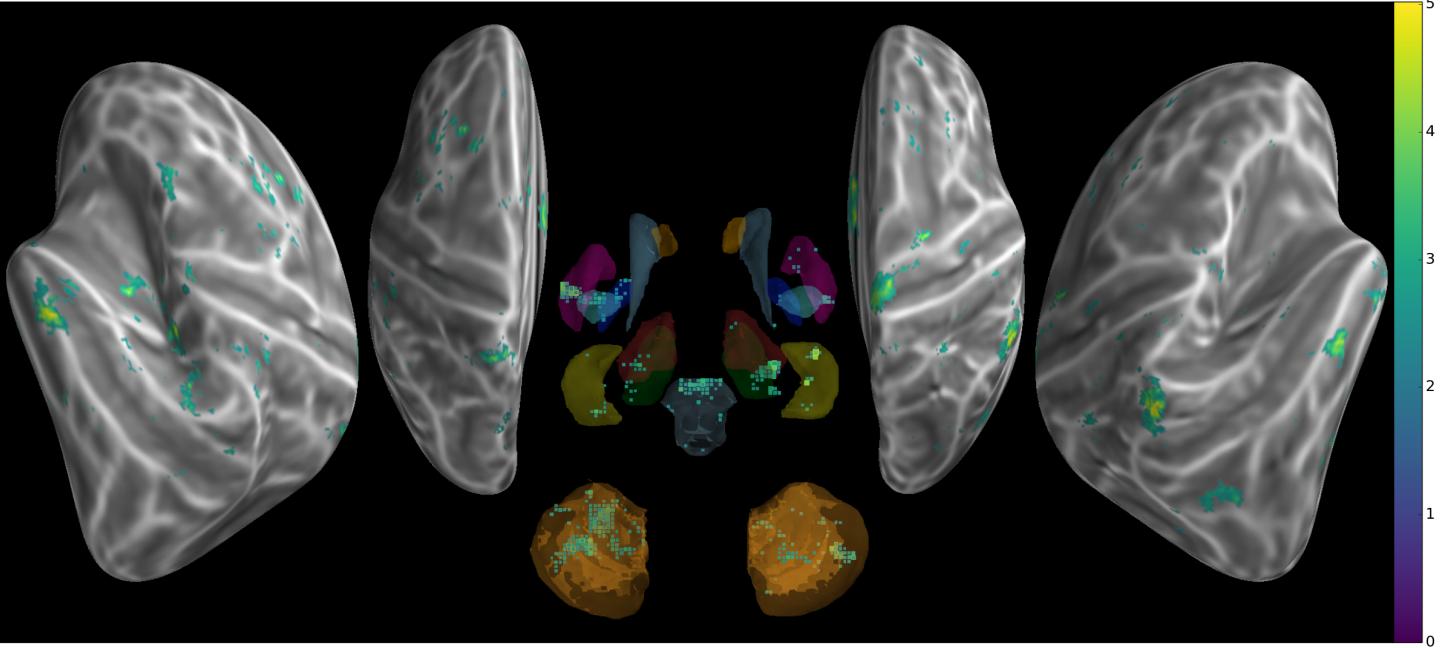


Figure 4: Contrast conjunction (trained-untrained, trained>chance) for Int accuracy during execution ($p<0.05$)

ROIS

Discussion

Using Searchlight even in a very controlled design gave individual maps with variability despite important common network found across subjects as highlighted by group analysis (fig). This raise an interest regarding potential causes of variable extended representation of sequences in each subject. As the task requires switching between different sequences, different strategies could be used by the subject to maintain in working memory the sequence first shown on the screen then practised physically.

Our group analysis revealed implication of a cortical network specific to sequences features, similar to (Wiestler and Diedrichsen 2013), as well as subcortical contributions to this representation.

TODO:

- representation of sequences characteristics and ROIs: (Kornysheva and Diedrichsen 2014)
- address all limitation and confounds (Todd, Nystrom, and Cohen 2013; Etzel, Zacks, and Braver 2013; Etzel, Cole, and Braver 2012) of MVPA and Searchlight

comparison with (Wiestler and Diedrichsen 2013):

- worst acquisition (12-channel, resolution...) but shorter TR.
- sequences not trained using same rapid-block design
- sequences not as intensively trained
- sequences at different stages of training/consolidation
- continuous execution of sequences
- using TRs (and GLM)

References

- Aguirre, Geoffrey Karl, Marcelo Gomes Mattar, and Lucía Magis-Weinberg. 2011. “De Bruijn Cycles for Neural Decoding.” *NeuroImage* 56 (3): 1293–1300. doi:10.1016/j.neuroimage.2011.02.005.
- Albouy, Genevieve, Stuart Fogel, Bradley R. King, Samuel Laventure, Habib Benali, Avi Karni, Julie Carrier, Edwin M. Robertson, and Julien Doyon. 2015. “Maintaining Vs. Enhancing Motor Sequence Memories: Respective Roles of Striatal and Hippocampal Systems.” *NeuroImage* 108 (March): 423–34. doi:10.1016/j.neuroimage.2014.12.049.
- Albouy, Geneviève, Bradley R. King, Pierre Maquet, and Julien Doyon. 2013. “Hippocampus and Striatum: Dynamics and

Interaction During Acquisition and Sleep-Related Motor Sequence Memory Consolidation.” *Hippocampus* 23 (11): 985–1004. doi:10.1002/hipo.22183.

Albouy, Geneviève, Virginie Sterpenich, Evelyne Balteau, Gilles Vandewalle, Martin Desseilles, Thanh Dang-Vu, Annabelle Darsaud, et al. 2008. “Both the Hippocampus and Striatum Are Involved in Consolidation of Motor Sequence Memory.” *Neuron* 58 (2): 261–72. doi:10.1016/j.neuron.2008.02.008.

Albouy, Geneviève, Virginie Sterpenich, Gilles Vandewalle, Annabelle Darsaud, Steffen Gais, Géraldine Rauchs, Martin Desseilles, et al. 2012. “Neural Correlates of Performance Variability During Motor Sequence Acquisition.” *NeuroImage* 60 (1): 324–31. doi:10.1016/j.neuroimage.2011.12.049.

———. 2013. “Interaction Between Hippocampal and Striatal Systems Predicts Subsequent Consolidation of Motor Sequence Memory.” *PLOS ONE* 8 (3): e59490. doi:10.1371/journal.pone.0059490.

Alexander, G. E., M. R. DeLong, and P. L. Strick. 1986. “Parallel Organization of Functionally Segregated Circuits Linking Basal Ganglia and Cortex.” *Annual Review of Neuroscience* 9: 357–81. doi:10.1146/annurev.ne.09.030186.002041.

Allefeld, Carsten, Kai Görgen, and John-Dylan Haynes. 2015. “Valid Population Inference for Information-Based Imaging: Information Prevalence Inference.” *ArXiv:1512.00810 [Q-Bio, Stat]*, December. <http://arxiv.org/abs/1512.00810>.

Avants, B. B., C. L. Epstein, M. Grossman, and J. C. Gee. 2008. “Symmetric Diffeomorphic Image Registration with Cross-Correlation: Evaluating Automated Labeling of Elderly and Neurodegenerative Brain.” *Medical Image Analysis*, Special Issue on The Third International Workshop on Biomedical Image Registration – WBIR 2006, 12 (1): 26–41. doi:10.1016/j.media.2007.06.004.

Barakat, Marc, Julie Carrier, Karen Debas, Ovidiu Lungu, Stuart Fogel, Gilles Vandewalle, Richard D. Hoge, et al. 2013. “Sleep Spindles Predict Neural and Behavioral Changes in Motor Sequence Consolidation.” *Human Brain Mapping* 34 (11): 2918–28. doi:10.1002/hbm.22116.

Battaglia, Francesco P., Karim Benchenane, Anton Sirota, Cyriel M. A. Pennartz, and Sidney I. Wiener. 2011. “The Hippocampus: Hub of Brain Network Communication for Memory.” *Trends in Cognitive Sciences* 15 (7): 310–18. doi:10.1016/j.tics.2011.05.008.

Beck, A. T., C. H. Ward, M. Mendelson, J. Mock, and J. Erbaugh. 1961. “An Inventory for Measuring Depression.” *Archives of General Psychiatry* 4 (June): 561–71.

Bednar, Jeffery G., Megan E. J. Campbell, and Ross Cunnington. 2015. “Basal Ganglia and Cortical Networks for Sequential Ordering and Rhythm of Complex Movements.” *Frontiers in Human Neuroscience* 9 (July). doi:10.3389/fnhum.2015.00421.

Born, Jan, and Ines Wilhelm. 2012. “System Consolidation of Memory During Sleep.” *Psychological Research* 76 (2): 192–203. doi:10.1007/s00426-011-0335-6.

Buckner, Randy L., Fenna M. Krienen, Angela Castellanos, Julio C. Diaz, and B. T. Thomas Yeo. 2011. “The Organization of the Human Cerebellum Estimated by Intrinsic Functional Connectivity.” *Journal of Neurophysiology* 106 (5): 2322–45. doi:10.1152/jn.00339.2011.

Buysse, Daniel J., Charles F. Reynolds III, Timothy H. Monk, Susan R. Berman, and David J. Kupfer. 1989. “The Pittsburgh Sleep Quality Index: A New Instrument for Psychiatric Practice and Research.” *Psychiatry Research* 28 (2): 193–213. doi:10.1016/0165-1781(89)90047-4.

Cellini, Nicola, and Elizabeth A. McDevitt. 2015. “The Temporal Dynamics of Motor Memory Across Wake and Sleep.” *The Journal of Neuroscience* 35 (35): 12085–7. doi:10.1523/JNEUROSCI.2429-15.2015.

Cousins, James N., Wael El-Deredy, Laura M. Parkes, Nora Hennies, and Penelope A. Lewis. 2014. “Cued Memory Reactivation During Slow-Wave Sleep Promotes Explicit Knowledge of a Motor Sequence.” *The Journal of Neuroscience* 34 (48): 15870–6. doi:10.1523/JNEUROSCI.1011-14.2014.

Dale, Anders M., Bruce Fischl, and Martin I. Sereno. 1999. “Cortical Surface-Based Analysis: I. Segmentation and Surface Reconstruction.” *NeuroImage* 9 (2): 179–94. doi:10.1006/nimg.1998.0395.

Dayan, Eran, and Leonardo G. Cohen. 2011. “Neuroplasticity Subserving Motor Skill Learning.” *Neuron* 72 (3): 443–54. doi:10.1016/j.neuron.2011.10.008.

Debas, Karen, Julie Carrier, Marc Barakat, Guillaume Marrelec, Pierre Bellec, Abdallah Hadj Tahar, Avi Karni, Leslie G. Ungerleider, Habib Benali, and Julien Doyon. 2014. “Off-Line Consolidation of Motor Sequence Learning Results in Greater Integration Within a Cortico-Striatal Functional Network.” *NeuroImage* 99 (October): 50–58. doi:10.1016/j.neuroimage.2014.05.022.

Debas, Karen, Julie Carrier, Pierre Orban, Marc Barakat, Ovidiu Lungu, Gilles Vandewalle, Abdallah Hadj Tahar, et al. 2010. “Brain Plasticity Related to the Consolidation of Motor Sequence Learning and Motor Adaptation.” *Proceedings of the National*

- Academy of Sciences* 107 (41): 17839–44. doi:10.1073/pnas.1013176107.
- Diedrichsen, Jörn, and Amy J. Bastian. 2014. “Cerebellar Function.” In *The Cognitive Neurosciences, Fifth Edition*. MIT press.
- Doyon, Julien, and Habib Benali. 2005. “Reorganization and Plasticity in the Adult Brain During Learning of Motor Skills.” *Current Opinion in Neurobiology*, Cognitive neuroscience, 15 (2): 161–67. doi:10.1016/j.conb.2005.03.004.
- Doyon, Julien, Pierre Bellec, Rhonda Amsel, Virginia Penhune, Oury Monchi, Julie Carrier, Stéphane Lehéricy, and Habib Benali. 2009. “Contributions of the Basal Ganglia and Functionally Related Brain Structures to Motor Learning.” *Behavioural Brain Research*, Special issue on the role of the basal ganglia in learning and memory, 199 (1): 61–75. doi:10.1016/j.bbr.2008.11.012.
- Doyon, Julien, Allen W. Song, Avi Karni, François Lalonde, Michelle M. Adams, and Leslie G. Ungerleider. 2002. “Experience-Dependent Changes in Cerebellar Contributions to Motor Sequence Learning.” *Proceedings of the National Academy of Sciences* 99 (2): 1017–22. doi:10.1073/pnas.022615199.
- Dudai, Yadin, Avi Karni, and Jan Born. 2015. “The Consolidation and Transformation of Memory.” *Neuron* 88 (1): 20–32. doi:10.1016/j.neuron.2015.09.004.
- Etzel, Joset A., Michael W. Cole, and Todd S. Braver. 2012. “Looking Outside the Searchlight.” In *Machine Learning and Interpretation in Neuroimaging*, edited by Georg Langs, Irina Rish, Moritz Grosse-Wentrup, and Brian Murphy, 26–33. Lecture Notes in Computer Science 7263. Springer Berlin Heidelberg. http://link.springer.com/chapter/10.1007/978-3-642-34713-9_4.
- Etzel, Joset A., Jeffrey M. Zacks, and Todd S. Braver. 2013. “Searchlight Analysis: Promise, Pitfalls, and Potential.” *NeuroImage* 78 (September): 261–69. doi:10.1016/j.neuroimage.2013.03.041.
- Fischl, B., M. I. Sereno, R. B. Tootell, and A. M. Dale. 1999. “High-Resolution Intersubject Averaging and a Coordinate System for the Cortical Surface.” *Human Brain Mapping* 8 (4): 272–84.
- Fischl, Bruce, Niranjini Rajendran, Evelina Busa, Jean Augustinack, Oliver Hinds, B. T. Thomas Yeo, Hartmut Möhlberg, Katrin Amunts, and Karl Zilles. 2008. “Cortical Folding Patterns and Predicting Cytoarchitecture.” *Cerebral Cortex* 18 (8): 1973–80. doi:10.1093/cercor/bhm225.
- Gerardin, Emmanuel, Jean-Baptiste Pochon, Jean-Baptiste Poline, Léon Tremblay, Pierre-François Van de Moortele, Richard Levy, Bruno Dubois, Denis Le Bihan, and Stéphane Lehéricy. 2004. “Distinct Striatal Regions Support Movement Selection, Preparation and Execution.” *Neuroreport* 15 (15): 2327–31.
- Glasser, Matthew F., Stamatios N. Sotiropoulos, J. Anthony Wilson, Timothy S. Coalson, Bruce Fischl, Jesper L. Andersson, Junqian Xu, et al. 2013. “The Minimal Preprocessing Pipelines for the Human Connectome Project.” *NeuroImage* 80 (October): 105–24. doi:10.1016/j.neuroimage.2013.04.127.
- Graybiel, Ann M. 1995. “Building Action Repertoires: Memory and Learning Functions of the Basal Ganglia.” *Current Opinion in Neurobiology* 5 (6): 733–41. doi:10.1016/0959-4388(95)80100-6.
- Gregory, Michael D., Yigal Agam, Chindhuri Selvadurai, Amanda Nagy, Mark Vangel, Matthew Tucker, Edwin M. Robertson, Robert Stickgold, and Dara S. Manoach. 2014. “Resting State Connectivity Immediately Following Learning Correlates with Subsequent Sleep-Dependent Enhancement of Motor Task Performance.” *NeuroImage* 102, Part 2 (November): 666–73. doi:10.1016/j.neuroimage.2014.08.044.
- Hanke, Michael, Yaroslav O. Halchenko, Per B. Sederberg, Stephen José Hanson, James V. Haxby, and Stefan Pollmann. 2009. “PyMVPA : A Python Toolbox for Multivariate Pattern Analysis of fMRI Data.” *Neuroinformatics* 7 (1): 37–53. doi:10.1007/s12021-008-9041-y.
- Hardwick, Robert M., Claudia Rottschy, R. Chris Miall, and Simon B. Eickhoff. 2013. “A Quantitative Meta-Analysis and Review of Motor Learning in the Human Brain.” *NeuroImage* 67 (February): 283–97. doi:10.1016/j.neuroimage.2012.11.020.
- Hikosaka, Okihide, Kae Nakamura, Katsuyuki Sakai, and Hiroyuki Nakahara. 2002. “Central Mechanisms of Motor Skill Learning.” *Current Opinion in Neurobiology* 12 (2): 217–22. doi:10.1016/S0959-4388(02)00307-0.
- Hotermans, Christophe, Philippe Peigneux, Alain Maertens de Noordhout, Gustave Moonen, and Pierre Maquet. 2006. “Early Boost and Slow Consolidation in Motor Skill Learning.” *Learning & Memory* 13 (5): 580–83. doi:10.1101/lm.239406.
- Howard, Marc W., and Howard Eichenbaum. 2015. “Time and Space in the Hippocampus.” *Brain Research*, Brain and Memory: Old Arguments and New Perspectives, 1621 (September): 345–54. doi:10.1016/j.brainres.2014.10.069.
- Jin, Xin, Fatuel Tecuapetla, and Rui M. Costa. 2014. “Basal Ganglia Subcircuits Distinctively Encode the Parsing and Concatenation of Action Sequences.” *Nature Neuroscience* 17 (3): 423–30. doi:10.1038/nrn.3632.
- Johns, M. W. 1991. “A New Method for Measuring Daytime Sleepiness: The Epworth Sleepiness Scale.” *Sleep* 14 (6): 540–45.
- Klein, Arno, Jesper Andersson, Babak A. Ardekani, John Ashburner, Brian Avants, Ming-Chang Chiang, Gary E. Christensen,

- et al. 2009. "Evaluation of 14 Nonlinear Deformation Algorithms Applied to Human Brain MRI Registration." *NeuroImage* 46 (3): 786–802. doi:10.1016/j.neuroimage.2008.12.037.
- Korman, Maria, Julien Doyon, Julia Doljansky, Julie Carrier, Yaron Dagan, and Avi Karni. 2007. "Daytime Sleep Condenses the Time Course of Motor Memory Consolidation." *Nature Neuroscience* 10 (9): 1206–13. doi:10.1038/nn1959.
- Kornysheva, Katja, and Jörn Diedrichsen. 2014. "Human Premotor Areas Parse Sequences into Their Spatial and Temporal Features." *eLife* 3 (August): e03043. doi:10.7554/eLife.03043.
- Kriegeskorte, Nikolaus, Rainer Goebel, and Peter Bandettini. 2006. "Information-Based Functional Brain Mapping." *Proceedings of the National Academy of Sciences of the United States of America* 103 (10): 3863–8. doi:10.1073/pnas.0600244103.
- Landry, Shane, Clare Anderson, and Russell Conduit. 2016. "The Effects of Sleep, Wake Activity and Time-on-Task on Offline Motor Sequence Learning." *Neurobiology of Learning and Memory* 127 (January): 56–63. doi:10.1016/j.nlm.2015.11.009.
- Laventure, Samuel, Stuart Fogel, Ovidiu Lungu, Geneviève Albouy, Pénélope Sévigny-Dupont, Catherine Vien, Chadi Sayour, Julie Carrier, Habib Benali, and Julien Doyon. 2016. "NREM2 and Sleep Spindles Are Instrumental to the Consolidation of Motor Sequence Memories." *PLOS Biol* 14 (3): e1002429. doi:10.1371/journal.pbio.1002429.
- Lee, Kyoung-Min, Kee-Hyun Chang, and Jae-Kyu Roh. 1999. "Subregions Within the Supplementary Motor Area Activated at Different Stages of Movement Preparation and Execution." *NeuroImage* 9 (1): 117–23. doi:10.1006/nimg.1998.0393.
- Lehéricy, Stéphane, Habib Benali, Pierre-François Van de Moortele, Mélanie Pélégrini-Issac, Tobias Waechter, Kamil Ugurbil, and Julien Doyon. 2005. "Distinct Basal Ganglia Territories Are Engaged in Early and Advanced Motor Sequence Learning." *Proceedings of the National Academy of Sciences of the United States of America* 102 (35): 12566–71. doi:10.1073/pnas.0502762102.
- Miyachi, Shigehiro, Okihide Hikosaka, and Xiaofeng Lu. 2002. "Differential Activation of Monkey Striatal Neurons in the Early and Late Stages of Procedural Learning." *Experimental Brain Research* 146 (1): 122–26. doi:10.1007/s00221-002-1213-7.
- Morin, Amélie, Julien Doyon, Valérie Dostie, Marc Barakat, Abdallah Hadj Tahar, Maria Korman, Habib Benali, Avi Karni, Leslie G. Ungerleider, and Julie Carrier. 2008. "Motor Sequence Learning Increases Sleep Spindles and Fast Frequencies in Post-Training Sleep." *Sleep* 31 (8): 1149–56. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2542961/>.
- Moser, May-Britt, David C. Rowland, and Edvard I. Moser. 2015. "Place Cells, Grid Cells, and Memory." *Cold Spring Harbor Perspectives in Biology* 7 (2): a021808. doi:10.1101/cshperspect.a021808.
- Mumford, Jeanette A., Benjamin O. Turner, F. Gregory Ashby, and Russell A. Poldrack. 2012. "Deconvolving BOLD Activation in Event-Related Designs for Multivoxel Pattern Classification Analyses." *NeuroImage* 59 (3): 2636–43. doi:10.1016/j.neuroimage.2011.08.076.
- Nambu, Isao, Nobuhiro Hagura, Satoshi Hirose, Yasuhiro Wada, Mitsuo Kawato, and Eiichi Naito. 2015. "Decoding Sequential Finger Movements from Preparatory Activity in Higher-Order Motor Regions: A Functional Magnetic Resonance Imaging Multi-Voxel Pattern Analysis." *European Journal of Neuroscience* 42 (10): 2851–9. doi:10.1111/ejn.13063.
- Nettersheim, Almut, Manfred Hallschmid, Jan Born, and Susanne Diekelmann. 2015. "The Role of Sleep in Motor Sequence Consolidation: Stabilization Rather Than Enhancement." *The Journal of Neuroscience* 35 (17): 6696–702. doi:10.1523/JNEUROSCI.1236-14.2015.
- Orban, Pierre, Julien Doyon, Michael Petrides, Maarten Mennes, Richard Hoge, and Pierre Bellec. 2015. "The Richness of Task-Evoked Hemodynamic Responses Defines a Pseudohierarchy of Functionally Meaningful Brain Networks." *Cerebral Cortex* 25 (9): 2658–69. doi:10.1093/cercor/bhu064.
- Orban, Pierre, Philippe Peigneux, Ovidiu Lungu, Geneviève Albouy, Estelle Breton, Frédéric Laberenne, Habib Benali, Pierre Maquet, and Julien Doyon. 2010. "The Multifaceted Nature of the Relationship Between Performance and Brain Activity in Motor Sequence Learning." *NeuroImage* 49 (1): 694–702. doi:10.1016/j.neuroimage.2009.08.055.
- Penhune, Virginia B., and Christopher J. Steele. 2012. "Parallel Contributions of Cerebellar, Striatal and M1 Mechanisms to Motor Sequence Learning." *Behavioural Brain Research* 226 (2): 579–91. doi:10.1016/j.bbr.2011.09.044.
- Pereira, Francisco, Tom Mitchell, and Matthew Botvinick. 2009. "Machine Learning Classifiers and fMRI: A Tutorial Overview." *NeuroImage* 45 (1, Supplement 1): S199–S209. doi:10.1016/j.neuroimage.2008.11.007.
- Press, Daniel Z., Melynda D. Casement, Alvaro Pascual-Leone, and Edwin M. Robertson. 2005. "The Time Course of Off-Line Motor Sequence Learning." *Brain Research. Cognitive Brain Research* 25 (1): 375–78. doi:10.1016/j.cogbrainres.2005.05.010.
- Raizada, Rajeev D S, and Yune-Sang Lee. 2013. "Smoothness Without Smoothing: Why Gaussian Naive Bayes Is Not Naive for Multi-Subject Searchlight Studies." *PloS One* 8 (7): e69566. doi:10.1371/journal.pone.0069566.
- Ramanathan, Dhakshin S., Tanuj Gulati, and Karunesh Ganguly. 2015. "Sleep-Dependent Reactivation of Ensembles in Motor

- Cortex Promotes Skill Consolidation.” *PLoS Biol* 13 (9): e1002263. doi:10.1371/journal.pbio.1002263.
- Rasch, Björn, and Jan Born. 2008. “Reactivation and Consolidation of Memory During Sleep.” *Current Directions in Psychological Science* 17 (3): 188–92. doi:10.1111/j.1467-8721.2008.00572.x.
- Roche, A. 2011. “A Four-Dimensional Registration Algorithm With Application to Joint Correction of Motion and Slice Timing in fMRI.” *IEEE Transactions on Medical Imaging* 30 (8): 1546–54. doi:10.1109/TMI.2011.2131152.
- Schlerf, J. E., T. D. Verstynen, R. B. Ivry, and R. M. C. Spencer. 2010. “Evidence of a Novel Somatotopic Map in the Human Neocerebellum During Complex Actions.” *Journal of Neurophysiology* 103 (6): 3330–6. doi:10.1152/jn.01117.2009.
- Stelzer, Johannes, Yi Chen, and Robert Turner. 2013. “Statistical Inference and Multiple Testing Correction in Classification-Based Multi-Voxel Pattern Analysis (MVPA): Random Permutations and Cluster Size Control.” *NeuroImage* 65 (January): 69–82. doi:10.1016/j.neuroimage.2012.09.063.
- Todd, Michael T., Leigh E. Nystrom, and Jonathan D. Cohen. 2013. “Confounds in Multivariate Pattern Analysis: Theory and Rule Representation Case Study.” *NeuroImage* 77 (August): 157–65. doi:10.1016/j.neuroimage.2013.03.039.
- Tseng, Ya-weng, Jörn Diedrichsen, John W. Krakauer, Reza Shadmehr, and Amy J. Bastian. 2007. “Sensory Prediction Errors Drive Cerebellum-Dependent Adaptation of Reaching.” *Journal of Neurophysiology* 98 (1): 54–62. doi:10.1152/jn.00266.2007.
- Ungerleider, Leslie G., Julien Doyon, and Avi Karni. 2002. “Imaging Brain Plasticity During Motor Skill Learning.” *Neurobiology of Learning and Memory* 78 (3): 553–64. doi:10.1006/nlme.2002.4091.
- Vahdat, Shahabeddin, Ovidiu Lungu, Julien Cohen-Adad, Veronique Marchand-Pauvert, Habib Benali, and Julien Doyon. 2015. “Simultaneous Brain–Cervical Cord fMRI Reveals Intrinsic Spinal Cord Plasticity During Motor Sequence Learning.” *PLOS Biol* 13 (6): e1002186. doi:10.1371/journal.pbio.1002186.
- Viswanathan, Shivakumar, Matthew Cieslak, and Scott T. Grafton. 2012. “On the Geometric Structure of fMRI Searchlight-Based Information Maps.” *ArXiv:1210.6317 [Q-Bio, Stat]*, October. <http://arxiv.org/abs/1210.6317>.
- Walker, Matthew P., Tiffany Brakefield, Joshua Seidman, Alexandra Morgan, J. Allan Hobson, and Robert Stickgold. 2003. “Sleep and the Time Course of Motor Skill Learning.” *Learning & Memory* 10 (4): 275–84. doi:10.1101/lm.58503.
- Wiestler, Tobias, and Jörn Diedrichsen. 2013. “Skill Learning Strengthens Cortical Representations of Motor Sequences.” *eLife* 2 (July): e00801. doi:10.7554/eLife.00801.
- Wiestler, Tobias, David J. McGonigle, and Jörn Diedrichsen. 2011. “Integration of Sensory and Motor Representations of Single Fingers in the Human Cerebellum.” *Journal of Neurophysiology* 105 (6): 3042–53. doi:10.1152/jn.00106.2011.
- Zang, Yufeng, Fucang Jia, Xuchu Weng, Enzhong Li, Shengzhong Cui, Yufeng Wang, Eliot Hazeltine, and Richard Ivry. 2003. “Functional Organization of the Primary Motor Cortex Characterized by Event-Related fMRI During Movement Preparation and Execution.” *Neuroscience Letters* 337 (2): 69–72. doi:10.1016/s0304-3940(02)01236-3.