

Group-wise Alignment of Resting fMRI in Space and Time

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ABSTRACT

Spontaneous brain activity is an important biomarker for various neurological and psychological conditions and can be measured using resting functional Magnetic Resonance Imaging (rfMRI). Since brain activity during rest is spontaneous, it is not possible to directly compare rfMRI time-courses across subjects. Moreover, the spatial configuration of functionally specialized brain regions can vary across subjects throughout the cortex limiting our ability to make precise spatial comparisons. We describe a new approach to jointly align and synchronize fMRI data in space and time across a group of subjects. We build on previously described methods for inter-subject spatial “Hyper-Alignment” and temporal synchronization through the “BrainSync” transform. We first describe BrainSync Alignment (BSA), a group-based extension of the pair-wise BrainSync transform, that jointly synchronizes resting or task fMRI data across time for multiple subjects. We then explore the combination of BSA with Response Hyper-Alignment (RHA) and compare with Connectivity Hyper-Alignment (CHA), an alternative approach to spatial alignment based on resting fMRI. The result of applying RHA and BSA is both to produce improved functional spatial correspondence across a group of subjects, and to align their time-series so that, even for spontaneous resting data, we see highly correlated temporal dynamics at homologous locations across the group. These spatiotemporally aligned data can then be used as an atlas in future applications. We explore the relative performance of BSA/RHA and CHA by computing spatial maps of inter-subject correlation of spatially aligned and synchronized rfMRI data. We also perform a validation study by applying the spatial transforms to z-score maps from an independent task fMRI dataset. Finally, we also explore application of these spatio-temporal alignment methods directly to task fMRI data.

Keywords: Group studies, Resting fMRI, Synchronization.

1. INTRODUCTION

Features derived from resting fMRI (rfMRI) data are increasingly being used as biomarkers for various neurological conditions, studying brain development, and investigating group differences¹. The states and timing of activity in dynamic functional networks in rfMRI, however, are not synchronized across subjects. This presents a challenge in investigating group differences and comparing dynamics directly from the rfMRI time series^{2,3}. Most studies analyze rfMRI by measuring functional connectivity between different brain regions through correlations computed from their time-series. Alternatively, group independent component analysis (ICA) can be used to decompose rfMRI data into either spatially or temporally independent components⁴. In common with correlation-based analysis, ICA approaches do not allow direct comparison of dynamics across subjects. Moreover, the spatial distribution of functional regions in the brain is variable across subjects and anatomical feature-driven cortical surface registration methods⁵⁻⁷ do not precisely align regions of functional specialization across subjects⁸. These limitations of existing methods has led to the development of alternative approaches that seek to perform spatial and/or temporal alignment using rfMRI data.

A series of recently developed techniques introduce a different perspective on group analysis of task and resting fMRI⁸⁻¹¹. These techniques apply an orthogonal linear transform to input fMRI data with respect to their temporal or spatial coordinates to generate a transformed representation that in some sense matches the data across subjects. Response HyperAlignment (RHA) aligns the subjects’ data spatially by applying a local orthogonal transform in the spatial domain to maximize the similarity of response profiles in a set of task fMRI data. RHA effectively uses linear combinations of signals in a local group of voxels from one subject to best approximate those in the same anatomical region in another subject or group average. This can be viewed as a method for functionally-based inter-subject spatial alignment that does not enforce any topological restrictions on the spatial mapping but instead uses linear combinations of the data from a local

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neighborhood in one subject to produce a spatial correspondence in the other⁹. Connectivity HyperAlignment (CHA)¹¹ is an extension of RHA for resting fMRI that uses connectivity profiles or a correlation matrix rather than the time-series themselves as a feature to perform spatial alignment. RHA and CHA can combine multiple local orthogonal transforms to perform spatial alignment of the entire cerebral cortex^{9,11}.

While the RHA and CHA techniques address spatial alignment, the BrainSync transform aligns subject data temporally by applying an orthogonal transform to the time series rather than spatially. BrainSync exploits the similar correlation structure in rfMRI data across subjects to align rfMRI, although it can also be applied to task fMRI¹⁰. The result of applying BrainSync is to modify the set of resting time-series for one subject so that they are approximately equal to those of the target subject or reference at homologous locations. As with RHA and CHA, BrainSync uses an orthogonal transform so that each element of the transformed time-series is a linear combination of the entire original time series. Topological or temporal contiguity constraints are not included in the transform. The common use of orthogonality constraints on the transforms in RHA, CHA and BrainSync make them all stable and invertible.

The purpose of this paper is two-fold. First, we describe a group extension of BrainSync, which we refer to as BrainSync Alignment (BSA). As described in Joshi et al (2018)¹⁰, BrainSync was applied pairwise to bring a group of subjects into alignment with a single representative subject. This tends to bias subsequent analysis towards the individual characteristics of the representative subject. Here we define a group approach in which orthogonal transforms are applied to each subject to match to an unbiased group average, which we also estimate, that can serve as a Joint Synchronized Group Average (JSGA) template.

The second goal of the paper is to explore combinations of spatial and temporal alignment. RHA performs spatial alignment of cortical locations using task fMRI but cannot align resting fMRI data due to the lack of temporal synchronization. On the other hand, BrainSync or BSA can be used to align spontaneous rfMRI data in time between any pair of subjects or to a group average. We can, therefore, combine them to perform simultaneous temporal and spatial group alignment of rfMRI data by first applying BSA than RHA. By applying this procedure to resting data of a large number of normal subjects, we can use the resulting group average template as a functional atlas against which we can compare other populations or task conditions. Moreover, we can use the transformation computed using RHA applied to BSA-transformed resting data to define a spatial-only transformation to be applied to independent task datasets of the same subjects. The combination of BSA and RHA can also be used with task as well as resting fMRI. In this case, even though data are temporally locked to a task or stimulus, differences in latency of response can lead to inter-subject variability in timing that can be reduced using the BSA transform. Here we explore whether RHA alignment of task data after application of BSA improves spatial functional correspondence compared to that obtained using RHA only. As a baseline, we also compared against spatial alignment using CHA in all cases. We evaluate performance using multiple rfMRI sessions and matched task fMRI data from the Human Connectome Project (HCP).

2. METHODOLOGY

We used RHA and CHA for spatial alignment and BSA for temporal alignment (synchronization) of subject data. All three methods find orthogonal transforms to align the input data to minimize the Frobenius norm as a distance measure. Although they share a similar form in terms of the cost function and are solutions to the general orthogonal Procrustes problem, they differ in the way that the information is used for synchronization or alignment as we describe below.

1.1 Preprocessing

As input, we assume structural and rfMRI images for each subject. The structural images are preprocessed to generate cortical surface representations and coregistered to a common atlas. The rfMRI data are preprocessed using HCPs minimal processing pipeline¹² and the time-series normalized to zero mean and unit temporal norm at each vertex. They are then mapped to the common cortical surface atlas. This preprocessing results in structurally coregistered $V \times T$ data matrices, X_k ($k = 1, 2, \dots, M$), one for each of M subjects, each with V vertices in the cortical surface mesh and T time points.

1.2 BrainSync Alignment (BSA)

After normalization of time-series at each vertex, each time-series can be represented as a point on a hypersphere. Under the assumption of similar spatial correlation patterns across subjects, it was previously shown that between every pair of subjects, there exists an orthogonal transform that approximately synchronizes their time series data¹⁰. In that work, a representative individual subject was chosen as a template for alignment. Here we describe an extension, BrainSync Alignment (BSA), that jointly finds a set of $T \times T$ orthogonal transforms O_i , $i = 1, 2, \dots, M$, such that the transformed

signals are jointly synchronized across subjects. Since the O_i transforms are invertible, this process preserves the full time-series and connectivity structure of the original data for all subjects. Each O_i is chosen such that it minimizes the joint cost $\sum_{i=1}^M \|X_i O_i - G\|^2$ where $G = (1/M) \sum_i X_i O_i$ is the group average computed from each of the aligned data sets. Interestingly, the solution to this problem is identical to that of finding the set of orthogonal transforms that minimize the sum of distances between each pair of transformed data sets¹³:

$$\arg \min_{O_i (i=1,2,\dots,M)} M \sum_{i=1}^M \|X_i O_i - G\|^2 = \sum_{j=1}^M \sum_{i < j} \|X_i O_i - X_j O_j\|^2 \quad (1)$$

The function can be optimized using a solution to the general orthogonal Procrustes problem¹⁴. For the $M = 2$ case, the orthogonal transform O_2 that rotates X_2 toward X_1 (with $O_1 = I$) is given by a closed form expression and can be calculated using a singular value decomposition (SVD) of the cross-correlation matrix: $O_2 = UV^t$ where $X_2^T X_1 = U \Sigma V^t$ ¹⁵. For solving the generalized form of Eq. (1) for $M > 2$, a closed form solution does not exist and an iterative solution is needed to obtain a minimum¹⁶. One solution is to use an alternating least-squares algorithm with the following steps: (i) G is initialized using a random set of initial orthogonal transforms O_i , $i = 1, 2, \dots, M$; (ii) Holding G constant, the left hand side of (1) decouples into separate problems for each $i = 1, 2, \dots, M$. The problem therefore reduces to the $M = 2$ case for each i and can be computed in closed form; (iii) G is then updated with the new O_i 's. Steps (ii) and (iii) are repeated until some convergence criterion is met. This iterative method is guaranteed to converge to at least a local minimum that depends on the initialization. It has also been proven that a sufficient condition for reaching the global minimum is that the cross covariance matrices for all pairs of transformed data are positive semidefinite after transformation^{13,14,16}.

As an alternative, Berge¹⁴ argued that including $X_k O_k$ in G in each step is suboptimal and that the k -excluded group average $G_k = \frac{1}{M-1} \sum_{i \neq k} X_i O_i$ would be a better alternative that results in convergence in fewer steps. Since $MG = X_k O_k + (M-1)G_k$, we obtain the identity:

$$\sum_{k=1}^M \|X_k O_k - G\|^2 = \left(\frac{M-1}{M}\right)^2 \sum_{k=1}^M \|X_k O_k - G_k\|^2 \quad (2)$$

so that using the k -excluded group average does not alter the solution of the optimization problem. Minimization of (2) can be performed iteratively using the same alternating method as outlined above but excluding the k^{th} dataset from each average for $k = 1, \dots, M$.

In our implementation of BSA, we initialize the O_i 's with a set of random orthogonal transformations and iteratively optimize them as above until we meet the convergence criterion that the relative change in the cost function is smaller than $1e-6$. We confirmed that using the k -excluded mean resulted in faster convergence. We ran this algorithm on multiple data sets with multiple random initializations and found that in practice for the rfMRI data the solutions were the same for all initializations, possibly indicating a globally optimal solution although the solutions did not satisfy the sufficiency condition above.

We refer to G as the Joint Synchronized Group Average (JSGA) template which can be used as a functional atlas representing typical resting functional activity across the group. Other subjects or groups can then be compared against this atlas (by also synchronizing them to G) as a means of identifying individual or group differences in spontaneous functional activity.

To visualize how well the JSGA represents the group of subjects from which it is computed, we used pairwise distances between subjects and the group average (the JSGA template) to perform a 2D multidimensional scaling (MDS) embedding and compare the position of the JSGA template to that of the best-fitting single subject template as described in Joshi et al (2018)¹⁰.

1.3 Response and Connectivity HyperAlignment (RHA, CHA)

In contrast to BSA which works on resting data, RHA assumes task data as input where timing is implicitly synchronized to a stimulus such as movie watching. The goal of RHA⁹ is to represent time series at each point on the cortex as a linear combination of other time series with a nominal 20 mm neighborhood such that the transformed data across subjects becomes similar within this region. Similarly to BSA, RHA also finds an orthogonal transform but in the spatial rather than temporal domain by minimizing the cost: $\sum_{i=1}^M \|X_i^T Q_i - H\|^2$ where $H = (1/M) \sum_i X_i^T Q_i$. To solve this optimization problem, RHA uses the following procedure: (i) one subject is aligned to an arbitrarily chosen reference subject; each additional subject is then transformed to the mean of all previously transformed subjects; (ii) each subject is then aligned

to the k -excluded mean from the previous pass; (iii) all subjects are realigned to the average from the second pass. Iterative repetition of step (iii) is equivalent to the algorithm for BHA outlined above but with a different initialization.

CHA applies a similar procedure as RHA but using connectivity profiles rather than the fMRI data itself. The connectivity profile is formed as the correlation from one vertex to all other vertices and used as the feature vector for that vertex from which the orthogonal transform is computed. The transform performs a Procrustes fit to maximize similarity in the spatial connectivity profiles across a group of subjects using a variant of the algorithm outlined for RHA. The orthogonal transforms in RHA and CHA both perform local spatial fits across subjects so that modifications are required to perform whole brain alignment as described by Haxby et al (2016)⁹ and Guntupalli et al (2018)¹¹.

1.4 Combination of BSA, CHA, RHA:

The limitation of RHA is that it needs stimulus locked input data and therefore cannot be used on spontaneous resting fMRI data. Since BSA can be used to align spontaneous rfMRI data to a group average, we can combine it with RHA to perform simultaneous temporal and spatial group alignment of rfMRI data by first applying BSA then RHA (jointly referred to below as BRHA). We note that BRHA can be applied to task fMRI as well as rfMRI. In the former case, this may have the advantage over RHA alone of aligning components in the brains response to a task that may vary in latency across subjects.

We computed spatial alignment transforms from the first session of resting data using both CHA¹¹ and the combination of BSA¹⁰ and RHA⁸ (or BRHA). We then applied these transforms to the second independent session after first temporally aligning the second session using BSA. We then calculated the correlation between each subject from the second session and the group average atlas. To further explore the impact of CHA and BRHA, we applied the spatial orthogonal transforms obtained from resting fMRI to z-score maps for the HCP task fMRI data for the same set of subjects and compared results using the inter-subject correlation (ISC). ISC was computed as the mean over all subjects of the correlation between each subject's z-score maps and the k -excluded mean of the other subjects. Larger ISCs should be indicative of improved functional correspondence across subjects in the task-related response as a result of CHA or BRHA's spatial alignment.

The different spatial alignment methods (RHA, CHA, BRHA) were also applied directly to task fMRI data. We used two sessions of several of the task data sets from the HCP database¹⁷. Orthogonal transforms were computed from the first session and applied to the second session of task data in each case. ISCs of the task time series were used for comparing results.

3. DATA

For spatio-temporal alignment of rfMRI, we used two 15-minute sessions of minimally preprocessed rfMRI data (TR = 720 ms, TE = 33.1 ms, 2 mm × 2 mm × 2 mm voxels) from 40 subjects in the Human Connectome Project (HCP) database¹² (all right-handed, age 26-30) in which the subjects were asked to relax and fixate on a projected bright cross-hair on a dark background. Data were resampled on the midcortical surface and coregistered to a standard cortical atlas. The data were then further down-sampled to an 11,000-vertex tessellation for computational tractability. CHA and BRHA transforms were calculated from the first session resting data and applied to the second after BSA transformation calculated independently for the second session. Z-score maps for the emotion (faces-shapes), gambling (punish-reward), language (math-story), motor (tongue-average), relational (matching-relational) and social (theory of mind) tasks in the HCP dataset¹⁷ (TR = 720 ms, TE = 33.1 ms, 2 mm × 2 mm × 2 mm voxels) for the same subjects were used for validation.

For spatio-temporal alignment of task fMRI data, we used two sessions of the motor (hand, foot, tongue movements), emotion (valance judgments (faces), shape recognition), and language (sentences, stories, mental arithmetic (auditory)) task data from the same 40 subjects as the rfMRI study¹⁷. Similar to the rfMRI processing, the minimally preprocessed task fMRI data was down-sampled to ~11k resolution. CHA, RHA and BRHA transforms obtained from the first session were then applied to the second session.

4. RESULTS

As shown in Figure 1(A), the JSGA template lies close to the center of the group in the MDS embedding, indicating that it is representative of the group. In comparison, the single subject template (#135932) lies off-center indicating a larger distance to some of the subjects in this group.

Figure 1(B) shows the mean correlation between time-series at homologous locations computed from the second session between each subject and the corresponding group average template. While BSA computed for the second session alone produces relatively high correlations after synchronization, these correlations are improved substantially when we also apply spatial alignment based on CHA or BRHA as computed from the first session. Furthermore, visual inspection indicates that BRHA leads to larger correlations than CHA.

Table 1 shows ISCs between z-score maps for the task data before and after spatial alignment using both CHA and BRHA computed from the first rfMRI session. Both CHA and BRHA produce significant improvements in ISCs relative to the original (non-aligned) data, indicating that spatial alignment based on resting data can lead to improved inter-subject alignment of independent task data. Interestingly, while the correlation plots in Figure 1(B) show improved correlation with BRHA relative to CHA, we found that while the differences are small, CHA performs significantly better than BRHA for language ($p < 0.0016$) and gambling ($p < 0.0016$) tasks using the Wilcoxon ranksum test Bonferroni-corrected for the six different tests in Table 1. Given the apparent discrepancy between Figure 1(B) and Table 1, further comparative studies of CHA and BRHA are needed to better understand their relative performance.

Results for spatio-temporal alignment using task fMRI data are summarized in Table 2 and illustrated in Figure 2 for three different tasks. Figure 2 shows increased ISCs using all three spatial alignment methods relative to the original data. BRHA significantly outperforms both RHA ($p < 0.0025$) and CHA ($p < 0.0025$) using the Wilcoxon ranksum test Bonferroni-corrected for the four different tests in Table 2. This result indicates the potential for the combination of BSA and RHA to provide overall improvements in alignment relative to either RHA or CHA alone when using task data.

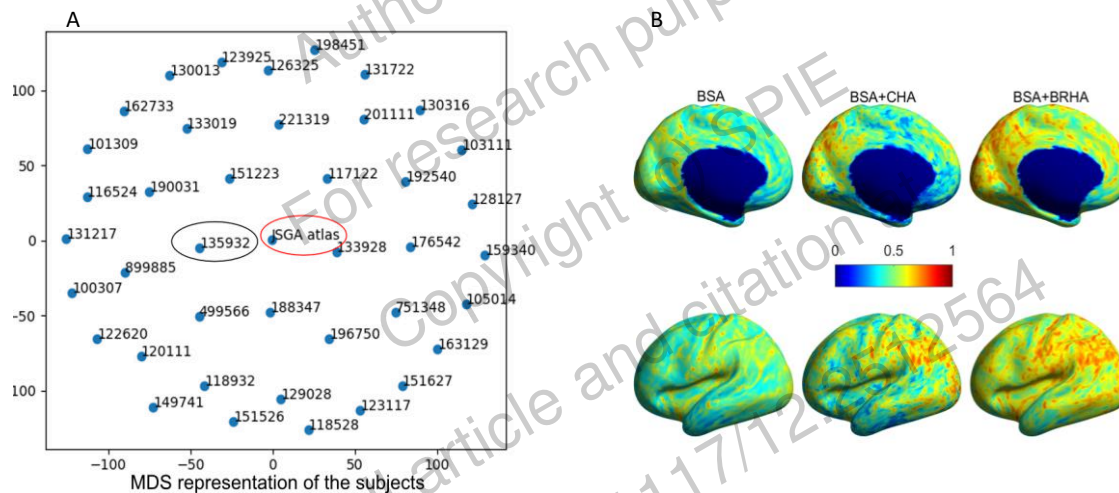


Figure 1. (A) MDS embedding of the 40 subjects and JSGA template based on the rfMRI data. The best representative individual template and the JSGA template are marked. (B) Mean correlation between subjects and group average templates for the second session data.

Table 1. Median and interquartile (in parenthesis) Inter Subject Correlations (ISCs) between response profiles of z-score maps before and after applying spatial transformations learned from resting fMRI.

Task	Contrast	Original	BRHA	CHA
Emotion	faces_shapes	0.5279(0.1227)	0.6025 (0.1222)	0.5954(0.1303)
Gambling	punish_reward	0.1337(0.0872)	0.1833(0.1727)	0.2161(0.2061)
Language	Math_story	0.6527(0.0850)	0.7428(0.0849)	0.7587(0.0852)
Motor	t_avg	0.4778(0.0913)	0.5275(0.1091)	0.5306(0.1130)
Relational	match_rel	0.3679(0.1833)	0.4542(0.2122)	0.4268(0.2450)
Social	random_tom	0.4626(0.1219)	0.5275(0.1357)	0.5236(0.1397)

5. CONCLUSION

The contribution of this work is twofold. First, we describe BSA, an extension of BrainSync that performs joint synchronization of rfMRI time-series across a group of subjects using a set of orthogonal transforms. This joint synchronization yields a group average template that can be used as a standard reference. Individual subjects can be compared to this reference to identify brain regions that do not synchronize well. This may be the case, for example, in epileptogenic regions in subjects with focal epilepsy.

The second contribution is the combination of BSA with RHA and CHA to perform simultaneous temporal and spatial synchronization of rfMRI data. We have shown that this combination increases the average correlation between individuals and the group average atlas relative to BSA alone, indicating the synergistic capabilities of combining spatial and temporal alignment. Using BRHA we were able to achieve similar performance to CHA when using the resulting transforms to align task fMRI data. We also investigated the application of BRHA and CHA directly to task data. Our results show that BRHA gives superior performance relative to either RHA or CHA alone, in terms of intersubject correlation after applying the computed transforms to matched independent task data from the same subjects. This approach may help reduce intrasubject differences across scans and improve power in group studies.

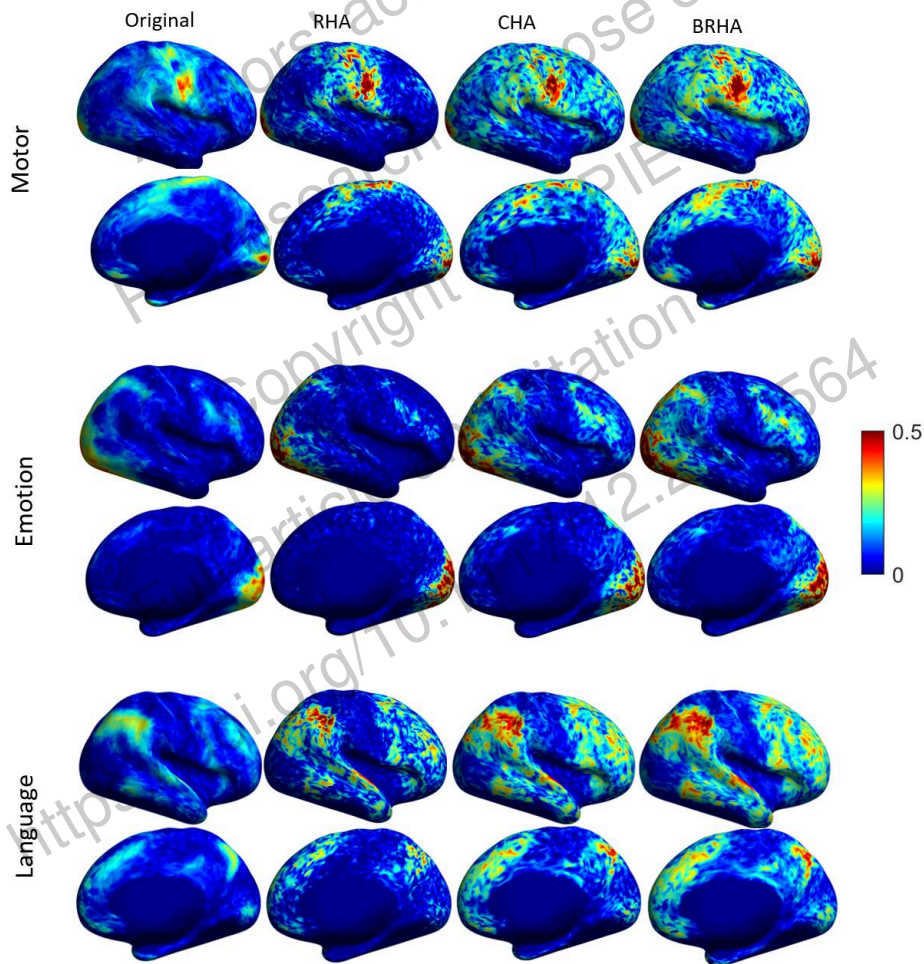


Figure 2. Mean of ISCs between response profiles for task data sets. Transforms were learned from the first task session and applied to the second.

Table 2. Median and interquartile (in parenthesis) of ISCs between response profiles of task fMRI datasets after applying spatial transformations learned from the first task session and applied to the second (MC: computed over Motor Cortex only, WC: computed over Whole Cortex).

Task	Original	RHA	CHA	BRHA
Motor(MC)	0.1739 (0.0323)	0.2110 (0.0690)	0.2107 (0.0531)	0.2394 (0.0584)
Motor(WC)	0.1009 (0.0328)	0.0936 (0.0377)	0.1369 (0.0437)	0.1502 (0.05)
Language(WC)	0.0800 (0.0273)	0.1037 (0.0355)	0.1333 (0.0465)	0.1464 (0.0470)
EMOTION(WC)	0.0657 (0.0238)	0.0601 (0.0239)	0.0966 (0.0325)	0.1089 (0.0372)

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