Heritability of hemodynamic response function of human brain during working memory task

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Introduction:

The hemodynamic response function (HRF) describes blood oxygenation level dependent (BOLD) signal changes in fMRI data and reflects blood flow changes coupled to neural activity. Neurovascular coupling is crucial for normal brain function but the contribution of genetic factors to coupling mechanisms is poorly understood. The twin paradigm, in which the degree of concordance between monozygotic (MZ, identical) and dizygotic (DZ, fraternal) twin pairs is compared, is an important way of identifying when genetic factors are important. Where inheritance makes a significant contribution to a trait, greater concordance is expected between monozygotic twin pairs than between dizygotic twin pairs. We investigated the heritability of the HRF in the brain using the twin methodology.

Methods:

Subjects fMRI data were acquired in 40 twin subjects, mean age 23.87 ± 2.27 S.D. years old. Subjects included 20 MZ twins (10 females, 10 males) and 20 DZ twins (10 females, 10 males).

Cognitive tasks Participants performed the 0- and 2-back versions of the N-back working memory task as previously described[1]. Stimuli were presented for 200 ms with 800 ms gaps. The participant performed each task (0, or 2-back) for 16 trials as one block. In total 16 alternating blocks were performed for two 0- and 2-back conditions (8 blocks/condition). The same fMRI session was repeated approximated 3 months later.

MR imaging The 3D T1-weighted and EPI images were acquired on a 4T Medspec whole body scanner (Bruker, Germany). The 3D T1-weighted images were acquired using an MPRAGE pulse sequence (TR = 2500 ms, TE = 3.83 ms, T1 = 1500 ms, pulse angle = 15, 0.89 × 0.89 × 089 mm). For each participant, 127 EPI images (TR = 2.1s, TE = 30 ms, flip angle = 90, 3.6 × 3.6 × 3.0 mm) were acquired continuously during the tasks.

Activated regions The fMRI data were analyzed using SPM8 (The Wellcome Trust Centre for Neuroimaging, London, UK) to determine the common activation voxels for the working memory task. Four regions [left and right middle frontal gyrus (MFG) and left and right angular gyrus, (AG)] (Fig. 1 a, b) that were significantly activated were selected for HRF modeling.

HRF modeling The time course of signal changes was averaged across activated voxels in each structure. A double gamma function with 5 parameters ($h(t) = A(\frac{t^{\alpha_1-1}\beta_1^{\alpha_1}e^{-\beta_1 t}}{\Gamma(\alpha_1)} - \frac{1}{6}\frac{t^{\alpha_2-1}\beta_2^{\alpha_2}e^{-\beta_2 t}}{\Gamma(\alpha_2)})$ was convolved with the boxcar function and fitted with the fMRI time course. The height (H), time to peak (T), and full width at half maximum (W) were estimated from the fitted HRF (Fig. 1c). Repeatability of HRF parameter estimates was also examined between the two scanning sessions.

HRF heritability Differences in H, T, and W within MZ twin pairs were compared with those within DZ pairs.

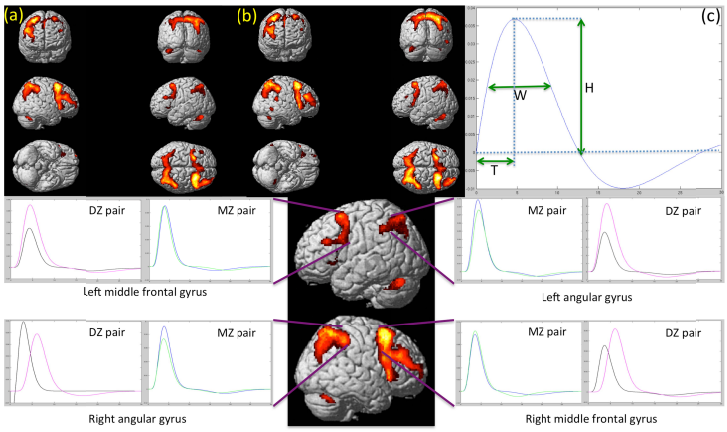

Fig. 1- (a, b) The common activated regions from experiment session 1 and 2, respectively. (c) The parameters estimated from HRF function. The lower row illustrates the estimated HRFs from a MZ pair and a DZ pair for four regions.

Results:

Similar activated regions were observed in the two experimental sessions (Fig. 1 a, b). The HRF differences of HRF shapes within MZ and DZ pairs are summarized in Table 1. Significantly smaller differences in T were observed in MZ compared to DZ pairs in Left MFG ($p < 0.04$), right MFG ($p < 0.01$), and in right AG ($p < 0.03$). There were consistently smaller differences in H between MZ twin pairs than in DZ twin pairs for all structures although none of the difference reached significance. The differences in W between MZ twin pairs were similar to those in DZ pairs.

Table 1 HRF difference between the MZ and DZ pairs[§]

Structures	ΔH (%)		ΔT (s)		ΔW (s)	
	MZ	DZ	MZ	DZ	MZ	DZ
Left MFG	0.021 ± 0.027	0.03 ± 0.024	0.513 ± 0.368	1.3875 ± 0.989	0.525 ± 0.772	1.013 ± 0.895
Right MFG	0.023 ± 0.027	0.04 ± 0.035	0.66 ± 0.44	1.353 ± 0.782	0.707 ± 0.758	1.393 ± 1.418
Left AG	0.02 ± 0.0185	0.043 ± 0.031	0.89 ± 0.737	0.96 ± 0.534	1.15 ± 1.521	0.89 ± 0.712
Right AG	0.023 ± 0.026	0.034 ± 0.033	0.639 ± 0.646	1.285 ± 0.668	1.223 ± 1.06	1.039 ± 0.855

§: ΔH, ΔT, and ΔW is the difference of HRF height, time to peak, and width at the half maximum within a pair of twin averaged across all twin pairs in percentage of signal change, in seconds, and in seconds, respectively.

Discussion:

The finding of a smaller difference in HRF time to peak in MZ twin pairs than DZ twin pairs suggests that this trait is heritable, perhaps reflecting the genetic influence on neurovascular coupling factors that control the timing of blood entry into the activated area. Width and height of the HRF did not show significant differences between MZ and DZ pairs perhaps reflecting a greater contribution of task-related factors.

Conclusion:

This is the first study demonstrating heritability of HRF parameters using fMRI data from a working memory task. Genetic influences on HRF time to peak were found.

References:

(1) Blokland GAM et al. *Biol. Psychol.* 2008 79: 70-79.