Title:

Frontoparietal pattern similarity analyses of cognitive control in monozygotic twins

Abbreviated Title:

Twin Similarity in Cognitive Control

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Abstract (247 words)

The ability to flexibly adapt thoughts and actions in a goal-directed manner appears to rely on cognitive control mechanisms that are strongly impacted by individual differences. A powerful research strategy for investigating the nature of individual variation is to study monozygotic (identical) twins. Clear evidence of twin similarity effects have been observed in prior behavioral and neuroimaging studies, yet within the domain of cognitive control, the specificity and neural underpinnings of this similarity remains elusive. Here, we utilize a multi-task, within-subjects event-related neuroimaging design (with fMRI) to investigate twin effects through multivariate pattern similarity analyses. We focus on a set of fronto-parietal brain parcels exhibiting consistently increased activation associated with cognitive control demands across four task domains: selective attention, context processing, multi-tasking, and working memory. In these parcels, healthy young adult male and female monozygotic twin pairs had similar activation patterns, reliably in all tasks, a finding not observed in unrelated pairs. Twin activation pattern similarity effects were clearest under high control demands, were not present in a set of task-unrelated parcels, and were primarily observed during the within-trial timepoints in which the control demands peaked. Together, these results indicate that twin similarity in the neural representation of cognitive control may be domain-general but also functionally and temporally specific in relation to the level of control demand. The findings suggest a genetic and/or environmental basis for individual variation in cognitive control function, and highlight the potential of twin-based neuroimaging designs for exploring heritability questions within this domain.

Significance Statement (120 words)

Cognitive control is indispensable to human adaptability. A critical goal for basic and translational research is to discover the brain basis of the individual differences that clearly characterize this domain. Neuroimaging studies of twins enable exploration of this issue, by identifying similarity and variation in task-evoked neural activity, and testing whether such effects are domain general, but also functionally specific to cognitive control demands. Here, we provide the first evidence of twin similarity in neural activation patterns within fronto-parietal regions, which is present in multiple cognitive control tasks, and selective to peak periods of control demand. These results confirm the domain-generality of neural representations of cognitive control, and support the genetic and/or environmental basis of this source of individual variation.

Introduction (635 words)

Cognitive control refers to the ability to regulate, coordinate, and sequence thoughts and actions in accordance with internally maintained goals (Braver, 2012). Convergent theoretical and empirical work suggests that cognitive control is a domain-general capacity (Duncan, 2010), involving mental processes spanning multiple domains of cognition, with shared neural representations within the fronto-parietal network (FPN) (Braver et al., 2009; Miller & Cohen, 2001; Miyake et al., 2000). Impairment in cognitive control is often detrimental to human functioning (Braver et al., 2002; Synder et al., 2015; McTeague et al., 2016; Barch & Sheffield, 2017). Consequently, identifying sources of individual variation in cognitive control function is

of theoretical and translational importance, for example, as a first step towards identifying critical intervention targets.

Twin-based designs provide an opportunity to examine potential sources of individual variation in cognitive control: if cognitive control is heritable, then its variability should at least be partially explained by genetic and environmental relatedness. In particular, monozygotic twins should exhibit the highest levels of similarity, as they share 100% of segregated loci and similar environments (Polderman et al., 2015). Indeed, in an influential behavioral study, using a twin-based multi-task design, individual differences in cognitive control function were shown to be almost entirely genetic in origin (Friedman et al., 2008).

Recent neuroimaging studies have utilized twin-based designs to suggest heritability of individual differences in some domains of cognitive control. In a series of large-scale studies, Blokland and colleagues (2008, 2011, 2017) demonstrated significant heritability effects on brain activation patterns within the FPN during a working memory task (N-back). Several small-scale twin neuroimaging studies showed convergent evidence of heritability in working memory and executive control (Koten et al., 2009; Matthews et al., 2007).

A powerful approach that is starting to be used in twin neuroimaging studies is that of multivariate pattern similarity analysis. This approach enables computation of a clear and compact quantitative metric that indicates the degree of similarity in neural activation patterns between paired individuals. Reliable twin activation similarity effects have been observed in functionally selective brain regions during visual tasks, such as the fusiform face area (Polk et al., 2007; Pinel et al., 2015). Utilizing the same approach, we recently demonstrated robust patterns of twin similarity in FPN activation patterns during N-back task performance in Human Connectome Project data (Etzel et al., 2020).

However, none of these prior studies demonstrated clear twin similarity within the domain of cognitive control, as they involved single tasks, and either focused on different domains, or did not selectively target cognitive control (e.g., N-back load manipulations may engage potentially different processes, such as working memory). Furthermore, as the prior studies utilized blocked experimental designs, they were unable to identify the temporal dynamics of twin similarity in neural activation patterns in relationship to task demands. Consequently, three key questions remain regarding twin similarity effects in neural activation patterns related to cognitive control. In particular, are these effects: 1) *domain-general (*or only observed in specific tasks, such as the N-back); 2) *anatomically specific* (i.e., preferentially observed in brain regions strongly associated with control demands); and 3) *temporally specific* (i.e., preferentially expressed during time periods of peak control demand)?

Here, we address these three questions by examining twin similarity in activation patterns across four prototypical task domains associated with cognitive control (selective attention, context processing, multi-tasking, and working memory), utilizing event-related designs and a task battery specifically developed for examining both intra- and inter-individual variation in cognitive control. We focused our examination of twin similarity on FPN brain parcels demonstrating consistent sensitivity to control demands in univariate contrasts in previous analyses (Braver et al., 2020). We then compared twin effects to those observed within a *null set* of parcels unengaged by cognitive control demands. Finally, we examined the time course of twin similarity effects within task trials to determine their potential temporal specificity.

Materials and Methods

Participants.

Healthy participants ranging from 18 to 45 years old were recruited from local communities for a multi-session behavioral and neuroimaging project - the Dual Mechanisms of Cognitive Control (DMCC) (Braver et al., 2020). As part of this project, twenty-eight pairs (56 participants) of monozygotic twins (46 females, mean age= 31.70 years, SD= 7.17) were recruited via the Human Connectome Project (Van Essen et al., 2013), Missouri Family Registry, and neighborhood flyers. Using all 56 twin participants and a group of 38 unrelated participants from the same DMCC project, we also generated 47 pairs of unrelated individuals (94 participants), who were of the same sex and within 2 years of age within each pair (62 females, mean age= 31.85 years, SD= 6.03). All participants were screened and excluded if they were diagnosed with mental illness, neurological trauma, or MRI safety contraindications. The full listing of exclusion criteria can be found at the following link (https://osf.io/6efv8/). Participants provided written informed consent and received $400 compensation (plus a $10 maximum task performance bonus) for completing all sessions. All study protocols were approved by the Institutional Review Board at Washington University.

Imaging Acquisition.

All imaging data were acquired at Washington University in St. Louis on a Siemens 3T PRISMA scanner using a 32-channel head coil. High-resolution MPRAGE anatomical scans (T1- and T2-weighted, voxel size=0.8 mm isotropic, TR=2400 msec for T1 and 3200 msec for T2) and BOLD functional scans (voxel size=2.4 mm isotropic, TR=1200 msec), were acquired using the CMRR multi-band sequences (acceleration factor=4, alternating AP and PA encoding directions, no in-plane acceleration). A full description of the acquisition protocol and parameters can be found at the following link (https://osf.io/tbhfg/).

Experimental Design and Statistical Analyses.

Procedure and Task Design.

All participants underwent four sessions (one behavioral, three neuroimaging) in the DMCC study. In the behavioral session, participants completed self-report measures of personality and psychological health, cognitive assessments of crystallized and fluid intelligence, and other relevant cognitive domains. In each of the three neuroimaging sessions, the same four tasks were performed, but with different experimental manipulations and conditions applied. The present analysis only uses data from the first (Baseline) neuroimaging session, as this session includes task variants specifically designed to capture individual differences in cognitive control, while also avoiding practice effects that might be present in the subsequent two sessions. Participants performed each task across two consecutive BOLD scanning runs (8 task runs total per session), each approximately 12 minutes in duration. The task order was randomized across participants, but to facilitate twin-based comparisons, the task order was the same for both members of a twin pair.

Participants were scanned while performing four well-established cognitive control tasks: Stroop, AX-CPT, Cued Task-Switching, and Sternberg Working Memory. In all tasks except the Stroop, participants responded with a manual response box inside the scanner, using index and middle fingers of the right hand. In the Stroop, participants made vocal responses that were recorded through a microphone. Prior to performing the tasks inside the scanner, participants practiced a short block of each task on a computer using a button box with the same key mapping

as the scanner response box. For Stroop, they were asked to say each response out loud. All tasks were programmed and presented to participants using Eprime software (Version 2.0, Psychology Software Tools, Pittsburgh, PA). In the following section, we briefly describe each task and its key contrasts. Additional description of each task condition and associated theoretical rationale can be found in Braver et al. (2020); a detailed listing of all task stimuli and parameters can be found at the following link (https://osf.io/48aet/).

Stroop. The color-word Stroop is widely recognized as a canonical task of cognitive control (Stroop, 1935; Egner & Hirsch, 2005), in which top-down selective attention is required to focus processing on the task-relevant font color of printed words, while ignoring the irrelevant but otherwise dominant word name. In the current version of the task, participants were asked to name the font color of the word (red, purple, blue, yellow, white, pink, black or green) out loud. Because of the large number of different responses (8), the task was implemented with vocal rather than manual responding. The Stroop interference effect, which contrasts incongruent (word name indicates a different color than the font color, e.g., BLUE in red font) and congruent (word name matches font color, e.g., BLUE in blue font) trials (see Figure 1A) was the key contrast. We employed a proportion congruence (PC) manipulation (Bugg et al., 2008), such that high PC was used for a set of stimuli (i.e. biased trials). Under high PC conditions, congruent trials are frequent and incongruent trials are rare, producing robust Stroop interference and individual differences effects (Kane & Engle, 2003). In our task fMRI analysis, biased incongruent trials were assumed to have high cognitive control demands, while biased congruent trials had low demands.

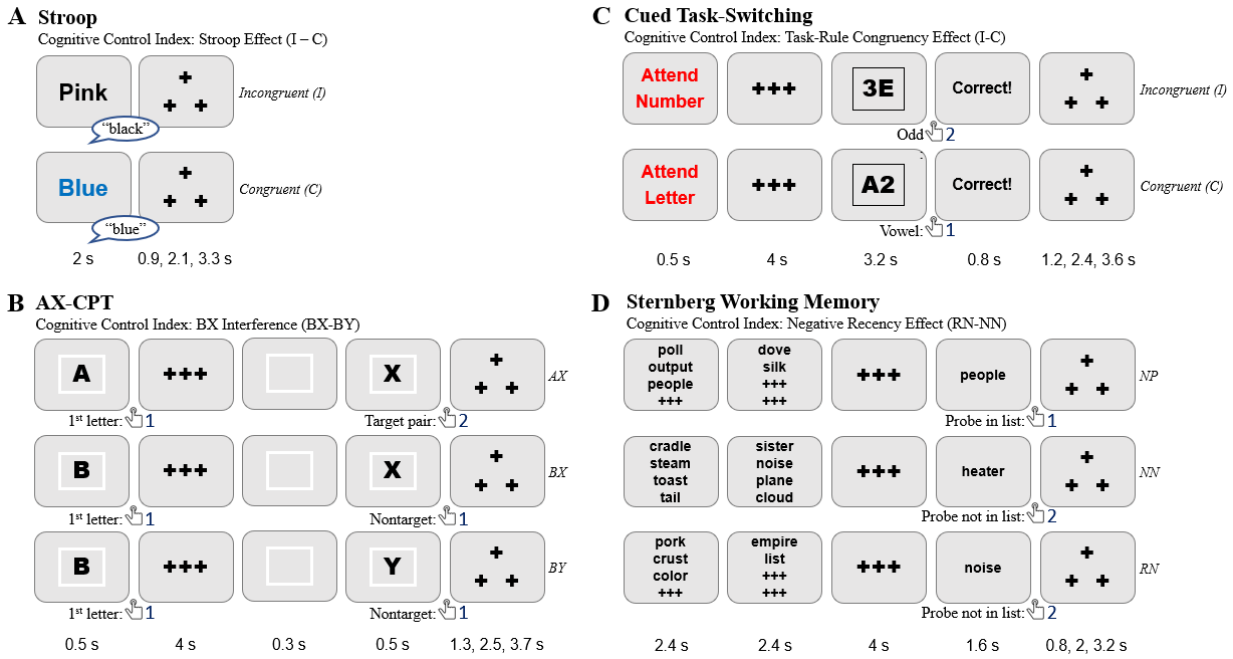
AX-CPT. The AX-CPT is increasingly used as a task of context processing and cognitive control, given its simplicity, flexibility and applicability in a wide-range of populations (Barch et al., 2008; Chatham et al., 2009; Chun et al., 2018; MacDonald, 2008; Paxton et al., 2007). In the task, participants were asked to respond to a pair of letters through button presses, with the first letter defined as a cue, followed by a second letter (sometimes a number), defined as a probe. The AX trials (A cue followed by an X probe) are the target response in the task, and occur with high frequency, leading to strong cue-probe associations. Cognitive control is postulated as a key process involved in maintaining and utilizing the contextual cue information, in order to minimize errors and response interference occurring on BX trials, which occur when the X-probe is presented but not preceded by an A-cue. Thus, a useful index of cognitive control for this task is the BX interference effect, which contrasts BX and BY (neither an A-cue nor an X-probe is presented, leading to low control demands) trial types (see Figure 1B). In our task fMRI analysis, BX trials were assumed to have high cognitive control demands, while BY trials had low demands.

Cued-TS. Cued task-switching (Cued-TS) has long been recognized as a critical paradigm to assess a core component of cognitive control – the ability to update and activate task-representations in an on-line manner to appropriately configure attention and action systems for processing the upcoming target (Kiesel et al., 2010; Meiran, 1996; Vandierendonck et al., 2010). In the task, participants were asked to respond to letter-digit target stimuli using button presses, with the target defined by the advance task cue (Letter or Digit). In the letter task, they were asked to decide if the letter is a consonant or a vowel. In the digit task, they were asked to decide if the digit is odd or even. An important index of cognitive control in task-switching paradigms is the task-rule congruency effect (TRCE; Meiran & Kessler, 2008), which refers to the increased interference (both errors and reaction time) when the response required for the current task trial

is different than the response that would be required (to the same target stimulus) if the other task had been cued (see Figure 1C). In letter-digit task-switching (also called consonant-vowel, odd-even or CVOE; Minear & Shah, 2008; Rogers & Monsell, 1995), if a right button press is required for a consonant (left for a vowel) in the letter task, and a right button press for odd (left for even) in the digit task, then the "3E" target stimulus is incongruent and the "A2" target stimulus is congruent (since under either task, a left button press is correct). In this task, there were also two sets of stimuli. One set of stimuli were mostly congruent (80% congruent; 20% incongruent), whereas the other set were unbiased (50% congruent, 50% congruent). Thus, to maximize individual differences, we used the biased set of stimuli in our task fMRI analysis, where incongruent trials were assumed to have high cognitive control demands, while congruent trials had low demands.

Sternberg. The Sternberg item-recognition task has been one of the most popular experimental paradigms used to assess short-term / working memory for over 50 years (Sternberg, 1966). In the task, participants were asked to remember a list of words (5-8 words) and then respond to a probe word, using a button press to indicate whether the probe word had been one of the words previously presented in the memory set for that trial. The Sternberg task has been adapted particularly for the study of cognitive control, and in neuroimaging paradigms, with the "recent probes" variant (Jonides et al., 1998; Jonides & Nee, 2006). In the recent probes variant, the key manipulation is that the probe item could have been a member of the memory set of the previous (not current) trial, which is termed a "recent negative" (RN) probe. On these RN trials, the probe is associated with high familiarity, which can increase response interference and errors, unless cognitive control is utilized to successfully determine that the familiarity is a misleading cue regarding probe status (target or nontarget). Thus, a key index of cognitive control in this Sternberg variant is the negative recency effect (Jonides & Nee, 2006; Monsell, 1978), which contrasts RN and NN trials (NN: novel negative, when the probe item is not a member of the current or previous trial's memory set; see Figure 1D). The current task has two sets of memory set items. One is the critical set of 5 words, whereas the other is the high-load set of 6-8 words. To maintain the same load length, we focused our task fMRI analysis on the critical set (5-item), where recent negative trials were assumed to have high cognitive control demands, while novel negative critical trials had low demands.

Figure 1. Diagram of Cognitive Control Tasks in DMCC battery



Imaging Analyses.

All DICOM images were first converted to BIDS format (Gorgolewski et al., 2016) for each participant using in-house scripts (https://hub.docker.com/u/ccplabwustl) and subsequently preprocessed using FMRIPREP version 1.3.2 (Esteban et al., 2018; RRID: SCR_016216), a Nipype (Gorgolewski et al., 2011; RRID:SCR_002502) based tool. Each T1w (T1-weighted) volume was corrected for INU (intensity non-uniformity) using N4BiasFieldCorrection v2.1.0 (Tustison et al., 2010) and skull-stripped using antsBrainExtraction.sh v2.1.0 (using the OASIS template). Brain surfaces were reconstructed using recon-all from FreeSurfer v6.0.1 (RRID: SCR_001847), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (Klein et al., 2017; RRID: SCR_002438). Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c (RRID: SCR_008796) was performed through nonlinear registration with the antsRegistration tool of ANTs v2.1.0 (RRID: SCR_004757), using brain-extracted versions of both T1w volume and template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (FSL v5.0.9, RRID: SCR_002823).

Functional data were slice time corrected using 3dTshift from AFNI v16.2.07 (RRID: SCR_005927) and motion corrected using mcflirt (FSL v5.0.9). Distortion correction was performed using 3dQwarp (AFNI v16.2.07). This was followed by co-registration to the corresponding T1w using boundary-based registration with six degrees of freedom, using bbregister (FreeSurfer v6.0.1). Motion correcting transformations, field distortion correcting warp, BOLD-to-T1w transformation and T1w-to-template (MNI) warp were concatenated and applied in a single step using antsApplyTransforms (ANTs v2.1.0) using

Lanczos interpolation. Following FMRIPREP preprocessing, additional pre-processing occurred with AFNI software (Cox, 1996), including a frame-wise motion censoring (FD > 0.9 mm) and image normalization (i.e., demeaning).

Five participants failed behavioral quality control checks (e.g. more than 40% of trials and/or 5 trials in a row are not responded in one run of a task) and were excluded from analyses for the problematic task, that is, if participant failed quality control for one run of a task, both runs were excluded from analyses, as runs were concatenated in our analyses.

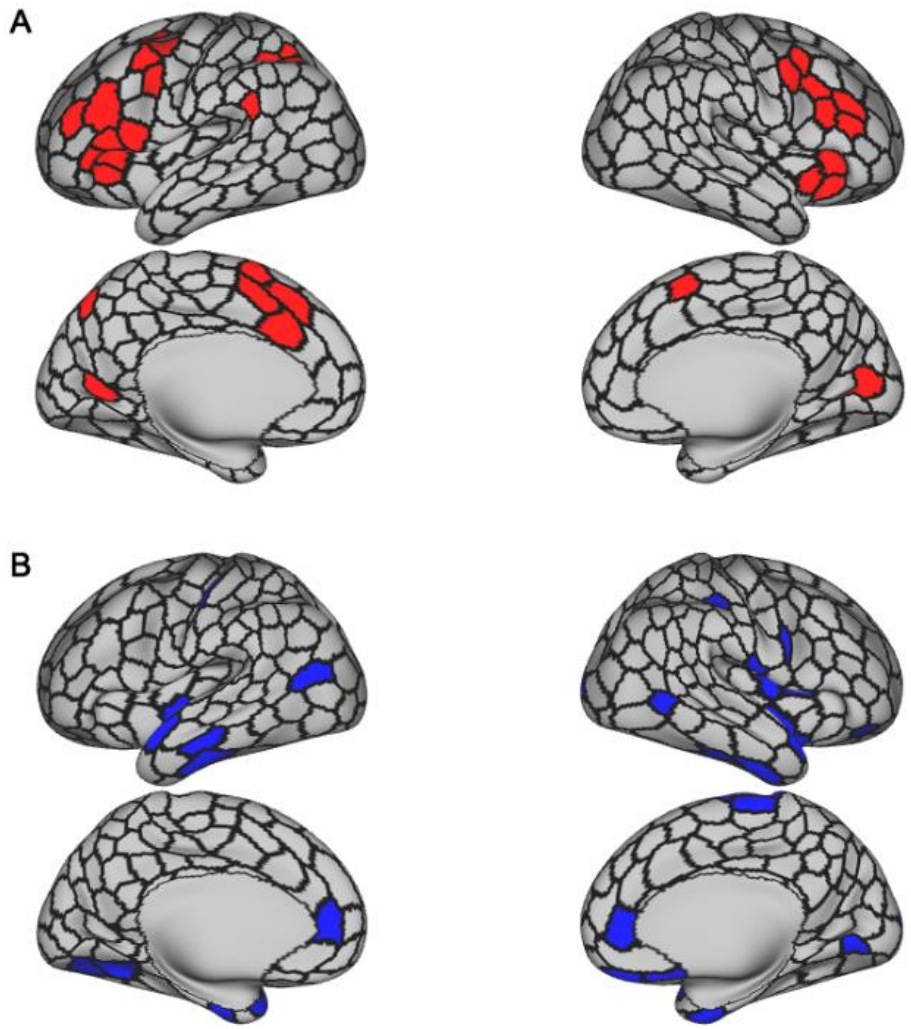
Univariate Analyses

After preprocessing, sustained and event-related effects were estimated using AFNI GLM functions (3dDeconvolve, 3dREMLfit) for each participant at the voxel-wise level (which includes 6-parameter motion and framewise censoring parameters, as well as polynomial detrending, using the -polort flag). The GLM estimation was conducted using a finite impulse response approach, implemented in AFNI using piecewise linear splines ("TENT" functions). This approach yielded an estimate of the full event-related time-course for each trial type. Timepoint estimates ("knots") were set to 1 knot per 2 TRs. Voxel-wise beta estimates were assigned into cortical parcels based on the Schaefer 400 parcels, 7 networks atlas (Schaefer et al., 2018), and subcortical parcels via the CIFTI FreeSurfer segmentation (19 nuclei) (Glasser et al., 2013). Within both the high demand and high minus low (i.e. high-low) demand contrasts, we focused on the 2-TR "target" knot expected to show maximal high > low activation difference during each trial, representing the peak of cognitive control demand (Braver et al., 2020).

Definition of Parcels of Interest

We have previously demonstrated robust cross-task high-low control demand contrast in the DMCC dataset (Braver et al., 2020), the results of which we used to identify the two sets of brain parcels for the current analysis: first, a target set of 34, primarily located within the fronto-parietal regions ("FPN34"- 6762 voxels, Figure 2A), with significant greater activation in the high than the low control demand condition within each of the four tasks. Second, for a negative control, we identified a set of 34 parcels ("NULL34" – 6656 voxels, Figure 2B) without a significant activation difference between high and low control demand conditions (i.e. null effect) in Braver et al., 2020, setting an insignificant threshold of $-1.5<t<1.5$ in each of the four tasks. As expected, this set of 34 control parcels was located in regions not generally associated with cognitive control. A full list of these two parcel sets with centroid coordinates can be found in the supplementary materials at the following link (https://osf.io/auxqs/).

Figure 2. FPN34 (A) and NULL34 (B) Parcel Sets from Schaefer 400 Parcellation (visualized on a surface-based template with parcel boundaries emphasized)



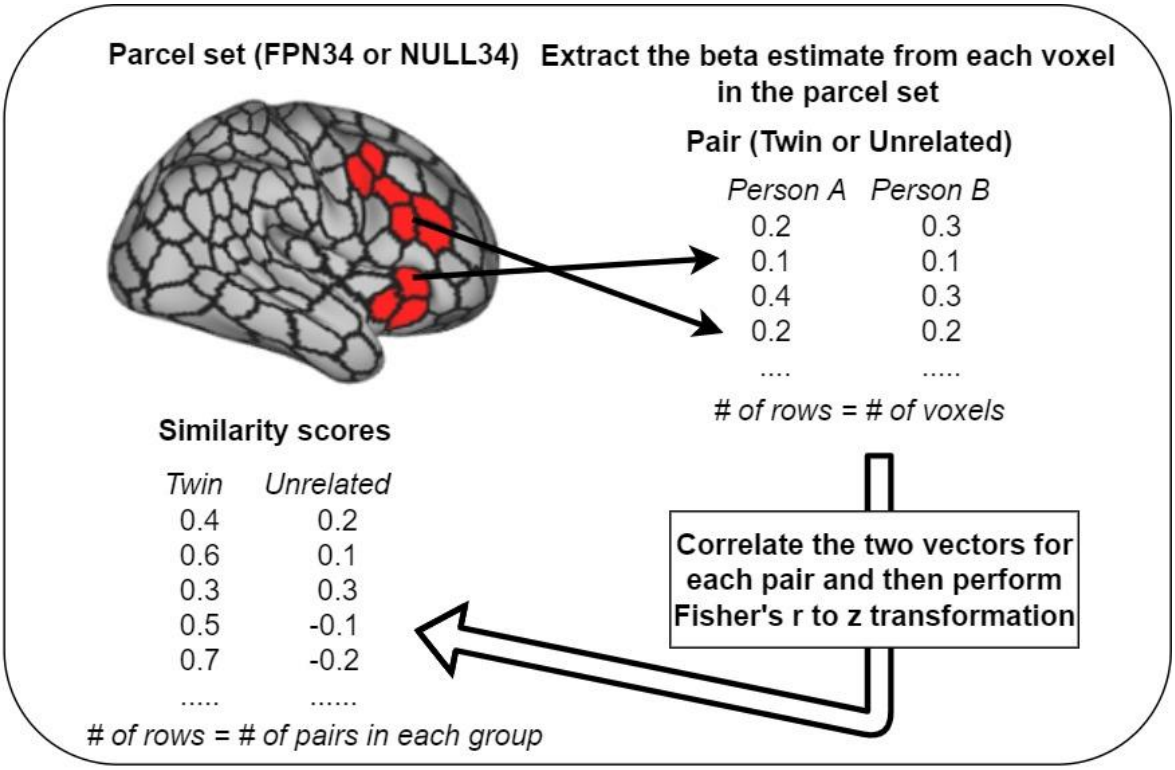
Multivariate Analyses – Twin Similarity

To compute twin similarity in activation patterns, we first extracted the beta estimates of all voxels for each person, each parcel set (FPN34 or NULL34), and each contrast (high control trials or high - low control contrast), at the target knot of each task. Next, for each task, we performed Pearson's correlations of vectors of beta estimates within each pair (twin or unrelated), separately for each contrast and each parcel set. Consequently, two vectors of similarity scores (i.e. correlation coefficients) were generated – one for all twin pairs and the other for all unrelated pairs. Figure 3 is a visualization of these steps of analyses.

In addition to examining the twin similarity at target knot, we are also interested in examining the temporal dynamics of twin similarity within task trials. Thus, we repeated the same steps shown in Figure 3, but at every 2-TR knot (i.e. timepoint) across task trials, not just the target knot. This allowed us to compare the activation patterns across the duration of a task trial to

examine the potential temporal dynamics of pattern similarity. We performed these time-course analyses within each task separately, as they varied in duration (i.e. different number of TRs).

Figure 3. A Flowchart of the Twin Similarity Analyses



Statistical Analyses

All analyses were performed using R version 3.6.3 (R Development Core Team 2015). Robust t-tests (Yuen, 1974) were conducted using the *DescTools* package (https://cran.r-project.org/web/packages/DescTools/index.html), with trimmed means (0.1 trim) to reduce the effects of outliers and non-normality. Linear mixed models were performed using the *nlme* package (https://cran.r-project.org/web/packages/nlme/index.html). Post-hoc contrasts of linear mixed models were conducted using the *lsmeans* package (https://cran.r-project.org/web/packages/lsmeans/index.html). The Fisher r-to-z transformation was applied to all correlation coefficients. Code for replicating the figures and analyses are available at the Open Science Foundation, https://osf.io/9d7ym/.

Results

Behavioral Task Performance.

We behaviorally validated that our trial type contrasts indexed cognitive control demands by analyzing RT and error rates across high and low control demand trials. Specifically, we tested the assumption that cognitive control demand would be associated with increased behavioral interference, observed as a decline in task performance, i.e., slower RTs and higher error rates present on high demand relative to low demand trials. To test for control demand effects, for

each task we conducted paired Yuen robust t-tests (two-tailed) on both error rates and RT (calculated from accurate trials only) in twins and unrelated individuals (i.e. does not include twins) separately.

As expected, we found highly robust interference effects (Table 1) in all four tasks, such that RT and error rates were higher on trials with high than low control demands. All effects were highly significant in twins: Stroop (RT: $t = 14.0$, $p<2.2 \times 10^{-16}$; error: $t = 3.2$, $p=0.004835$), AX-CPT (RT: $t = 6.6$, $p=5.3 \times 10^{-8}$; error rate: $t = 5.7$, $p=9.1 \times 10^{-7}$), Cued-TS (RT: $t = 5.7$, $p=8.1 \times 10^{-7}$; error: $t = 4.9$, $p=1.2 \times 10^{-5}$), Sternberg (RT: $t = 7.3$, $p=3.6 \times 10^{-9}$; error rate: $t = 11.2$, $p=1.7 \times 10^{-14}$). Similarly, all effects were significant in unrelated individuals: Stroop (RT: $t = 12.9$, $p=8.6 \times 10^{-14}$; error: $t = 3.8$, $p=0.0006633$), AX-CPT (RT: $t = 7.5$, $p=3.3 \times 10^{-8}$; error rate: $t = 4.9$, $p=3.2 \times 10^{-5}$), Cued-TS (RT: $t = 2.2$, $p=0.0317$; error: $t = 4.9$, $p=3.0 \times 10^{-5}$), Sternberg (RT: $t = 4.9$, $p=3.6 \times 10^{-5}$; error rate: $t = 5.9$, $p=2.1 \times 10^{-6}$). Together, these results support using these selected trial types to index high control and low control demand in each task.

We also compared the interference effects between twins and unrelated individuals by conducting two-sample robust t-tests (two-tailed) on RT and error rates. No significant difference in interference effects was detected in RT or error rates ($p>0.05$), except that the interference effect on error rates in Sternberg was greater in twins than in unrelated individuals ($t = 2.6$, $p=0.01156$). Together, the behavioral data suggest that twins and unrelated individuals responded to cognitive control demands in a mostly equivalent manner.

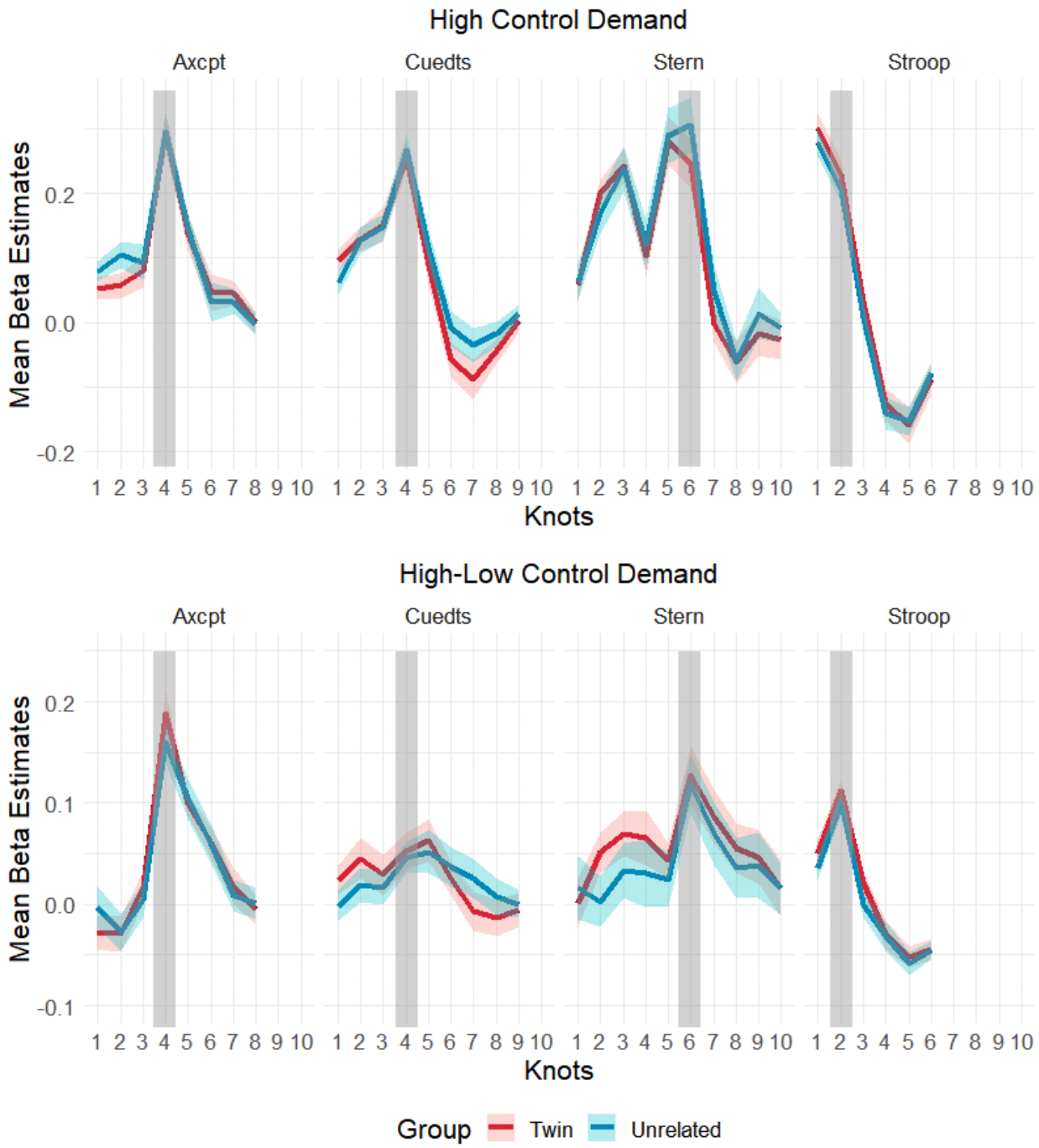
Table 1: Robust Mean (SEM) of Task Performance for High and Low Demand Trials in Twins and Unrelated Individuals

Tasks	Twins				Unrelated			
	High RT	Low RT	High Error	Low Error	High RT	Low RT	High Error	Low Error
Stroop	887 (20.3)	755 (18.6)	0.017 (0.005)	0.001 (0.001)	950 (23.2)	816 (20.5)	0.020 (0.006)	0.003 (0.001)
AX-CPT	587 (29.3)	456 (12.5)	0.138 (0.023)	0.018 (0.004)	615 (31.1)	464 (20.6)	0.172 (0.035)	0.028 (0.011)
Cued-TS	1090 (33.0)	1026 (33.2)	0.059 (0.010)	0.021 (0.004)	1194 (47.9)	1162 (41.6)	0.079 (0.014)	0.021 (0.006)
Sternberg	1095 (32.5)	901 (24.5)	0.304 (0.028)	0.039 (0.010)	1096 (41.8)	955 (34.8)	0.231 (0.033)	0.067 (0.023)

Timecourses of Neural Activations in Each Task.

As a first validation step, beta estimates from univariate analyses were extracted, and plotted as event-related timecourses for each group. Based on visual inspection of the timecourses of neural activation for both high control demand trials and high-low control contrast in twins and unrelated pairs (see Figure 4), it is clear that the two groups had equivalent neural activation in each task across all timepoints. To confirm this pattern, we conducted robust t-tests on the mean beta estimates of the two groups; as expected, there was no significant difference in activation between the two pair groups at any timepoint in each of the four tasks ($p>0.05$).

Figure 4. Robust Mean and SEM of Beta Estimates of Twins and Unrelated Pairs by Task

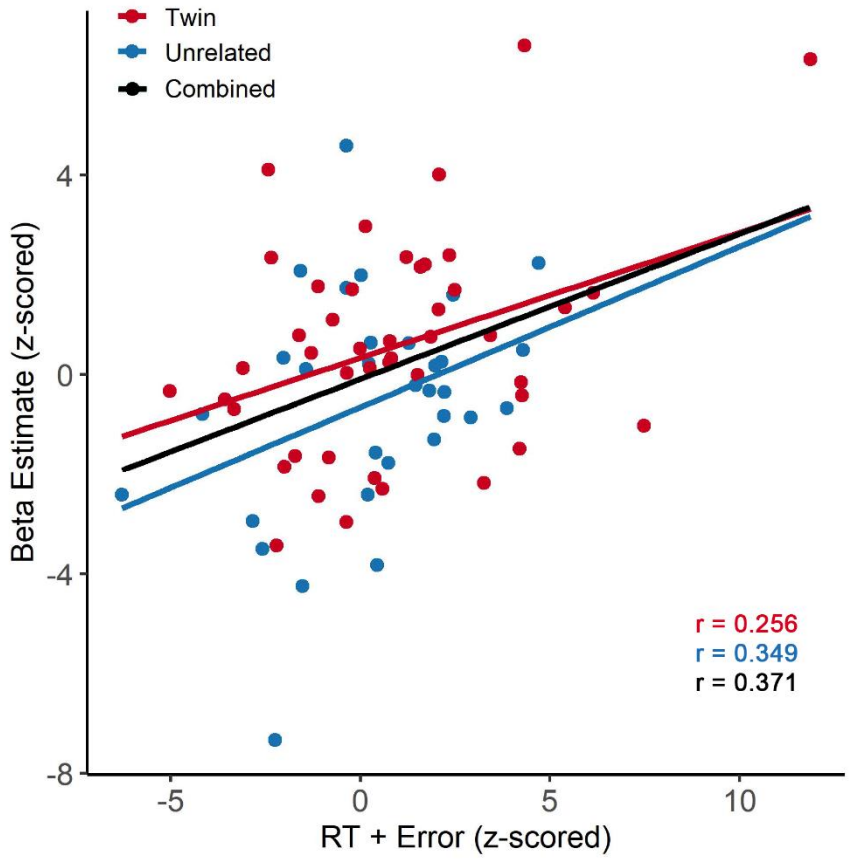


Brain-Behavior Relationship.

As a second validation step, we established the presence of functionally important individual variation related to cognitive control in this dataset. In a separate (but mostly overlapping) sample, we had previously observed a relationship between individual differences in neural activation levels (at the peak timepoint of cognitive control demand) and the magnitude of behavioral interference effects (Braver et al., 2020). We tested whether the pattern was also

observed in this sample, and was equally present across the twins and unrelated individuals. Unlike the previous analysis, this was conducted treating each individual separately (rather than as pairs). For the analysis, we created a composite behavioral index of performance, by z-score normalizing the data across individuals, and then combining RT and error measures across the four tasks to create a summed z-score value for each individual, with larger values indicating greater interference. Similarly, to create a composite neural activity index, we z-score normalized the mean beta estimate of FPN34 for high-low control contrast across individuals but separately for each task. We then summed these z-scores across the four tasks for each individual and correlated the behavioral and neural composites, yielding an overall positive correlation across the sample (r=0.371, p=0.000902). Further, the twin and unrelated individuals showed similar levels of correlation, which were not significantly different from each other (twins: r=0.256, unrelated: r=0.349; see Figure 5). Thus, the magnitude and direction of correlation replicated our previous findings (Braver et al., 2020). Additionally, these results confirm both the presence of meaningful individual variation in the sample, in terms of neural activity indexing cognitive control demand, and the functional relevance of neural activation in terms of its relationship to behavioral indicators of cognitive control function.

Figure 5. Brain-Behavior Relationship across Tasks



Twin Similarity in High Control Demand Trials.

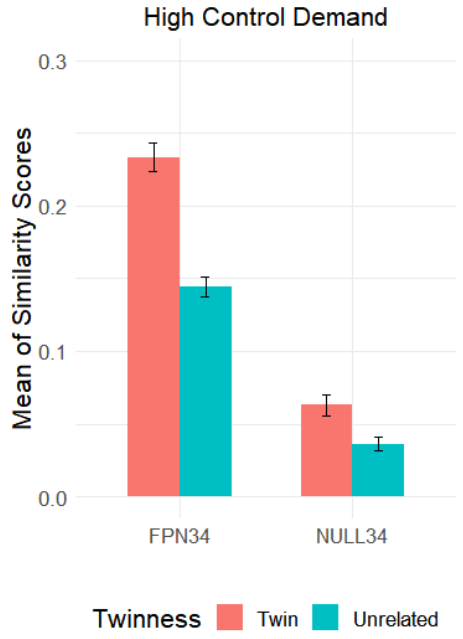
We next examined neural similarity patterns in the two pair groups, focusing initially on high control demand trials, through three inter-related analyses. First, we aggregated the similarity

scores across all four tasks to examine the overall effects of twinness (i.e. twins and unrelated) and parcel set (i.e. FPN34 and NULL34) on patterns of activation. Second, we broke down this analysis to compare similarity scores in each of the four tasks. Third, we examined the temporal dynamics of pattern similarity, by examining activation patterns similarity at each timepoint (2-TR knot) within the trial, for each of the four tasks.

Aggregating the similarity scores of all four tasks, we built a linear mixed model to test for the fixed effects of parcel set and twinness (i.e. whether the pair is twin or unrelated), as well as their interaction effect, on pattern similarity in high control demand trials. We also included task (AX-CPT, Cued-TS, Sternberg, and Stroop) and pair ID (all twin and unrelated pairs) as random effects in the model, to account for potential variance due to each individual pair and task. The detailed model set up can be found in the supplementary materials at the following link (https://osf.io/t2rf4/).

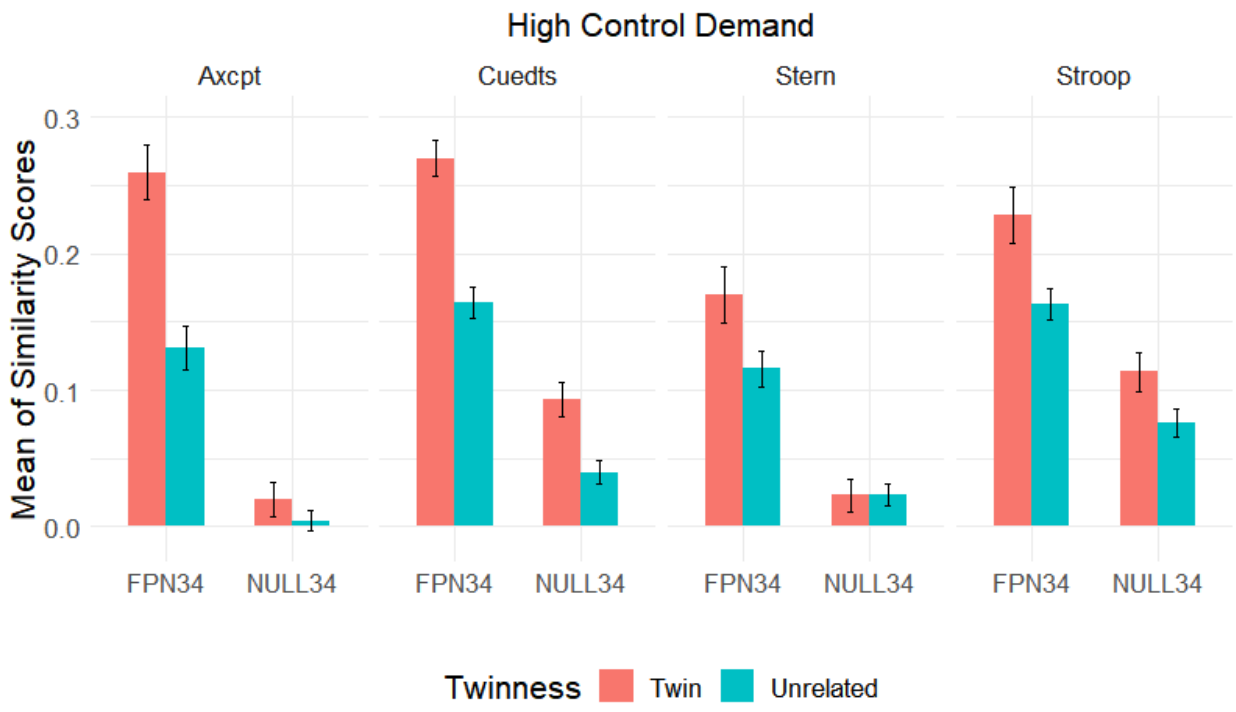
We identified a significant parcel set by twinness interaction ($p<0.0001$), which we further investigated with post-hoc contrasts. Specifically, we hypothesized that the interaction was due to a significant difference in similarity between the twin and unrelated pairs in the FPN34 parcel set, but not in the NULL34 parcel set, as NULL34 is not functionally relevant for cognitive control and should only exhibit arbitrary patterns of similarity within each pair. This hypothesis was mostly confirmed (see Figure 6), in that the similarity differences were highly significant in the FPN34 ($p_{corrected}<0.0001$). In particular, not only were overall similarity scores higher in the FPN34 parcel set relative to the NULL34 parcel set, but also the effect of twinness was significantly greater. However, in the NULL34 parcel, the effect of twinness, though much weaker than FPN34, was still marginally significant ($p_{corrected}=0.0468$). Nevertheless, the overall pattern suggests that the twin effect on pattern similarity in high control demand trials was primarily expressed in the FPN34 parcel set that was associated with cognitive control demand sensitivity.

Figure 6: Mean (and SEM) of Similarity Scores in High Control Demand Trials



We next examined the similarity of twins and unrelated individuals within each task separately, using a linear mixed model. The model and output for each task can be found in the supplementary materials at the following link (https://osf.io/rme3p/). In three of the four tasks (not in Stroop), the interaction of twinness and parcel set was statistically significant. We therefore carried out post-hoc analyses within each of the three tasks. Consistent with the trends we observed above, twins had significantly higher similarity in activation patterns than unrelated individuals in the FPN34 parcel set (see Figure 7) in AX-CPT ($p_{corrected}<0.0001$), Cued-TS ($p_{corrected}<0.0001$), and Sternberg ($p_{corrected}=0.021$). Conversely, similarity of activation patterns within the NULL34 parcel set did not differ significantly in AX-CPT or Sternberg. However, for Cued-TS, a significant difference was observed in the NULL34 parcel set ($p_{corrected}=0.0073$). For Stroop, although there was no significant interaction, we built two linear mixed models on FPN34 and NULL34 similarity scores respectively, with twinness (twins or unrelated) as the only fixed effect and pair ID as random effect in each model, to specifically examine the direction of our hypothesis regarding similarity difference between twins and unrelated pairs. Like in Cued-TS, we found significantly greater twin similarity relative to unrelated pairs in both FPN34 ($p=0.0041$) and NULL34 ($p=0.0304$) in Stroop. Overall, the results support the hypothesis that the twin effect was largely specific to the FPN34 parcel set, and absent or weaker in the NULL34 parcel set when examined separately in each task.

Figure 7: Mean (and SEM) of Similarity Scores in High Control Demand Trials by Task

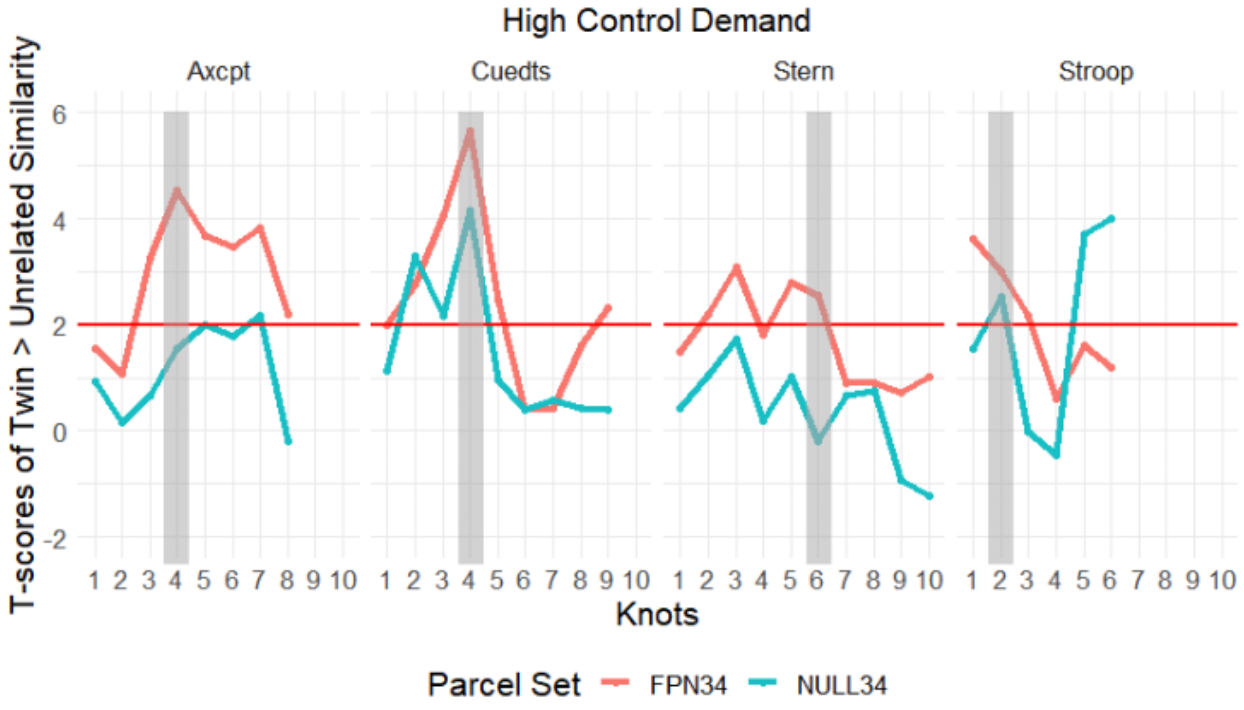


Temporal Dynamics of Twin Similarity: High Control Demand.

Next, we conducted a robust two-sample t-test (two-tailed) to compare similarity scores of twins and unrelated pairs at every timepoint estimate (2-TR knot) across each of the four tasks. The t-scores indicate the degree to which the neural pattern similarity of twins differs from that of

unrelated pairs, with higher t scores indicating greater differences and higher twin similarity. Here, linear mixed models were not carried out as we were interested in similarity differences between twins and unrelated for each parcel set individually, rather than the parcel set by twinness interaction. We plotted these t-scores across the task trials to illustrate the temporal dynamics of the twin similarity effect (see Figure 8), with the target timepoint (expected peak control demand) shaded in grey and a red line illustrating the statistical significance threshold ($p<0.05$). In all four tasks, the similarity scores at the target timepoint in these high control demand trials were significantly higher in twins than in unrelated pairs in the FPN34 parcel set. Notably, in AX-CPT and Cued-TS, the twin effect (i.e. twin > unrelated) peaked at the target timepoint relative to the other timepoints in the FPN34 parcel set. In Sternberg and Stroop, the twin effect was strong in the FPN34 parcel set, but did not peak at the target timepoint. Finally, except for Cued-TS, in which there was a peak at the target timepoint in the NULL34 parcel set, the twin effect in all tasks was rather weak and arbitrary in time, within the NULL34 parcel set across the task trials. Likewise, supporting the prior analyses, the twin effect was statistically weaker in NULL34 than FPN34 across most timepoints.

Figure 8: Temporal Dynamics of Difference in Pattern Similarity (Twin > Unrelated) in High Control Demand Trials



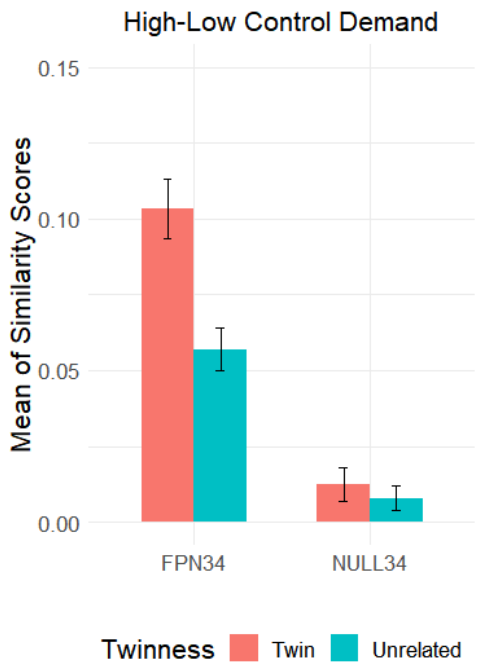
Twin Similarity in High-Low Control Demand.

In our next set of analyses, we conducted a more stringent examination of the twin similarity effect by examining neural activation patterns in terms of the high-low control demand contrast. Unlike the above analyses that focused only on high control demand trials, here we tested whether the differences in neural activation patterns between high and low control demand trials were also similar in twins and specific to the FPN34 parcel set. It should be noted that by doing so, we inevitably increase the amount of measurement error and impose stricter constraints on

the statistical analysis (i.e. looking for similarity in activation difference patterns). Thus, purely on a priori statistical grounds, this set of analyses would likely yield less robust results relative to those found when examining high control demand trials alone. Nevertheless, since this analysis more strongly isolates the effect of cognitive control demand itself (by removing activation variation due to general engagement on task trials), it provides a stronger test of our hypotheses.

Similar to the analyses performed in high control demand trials, we built a linear mixed model to examine the effects of twinness and parcel set when aggregating the four tasks, as well as their interaction effect on the similarity of activation patterns in the high-low control demand contrast. The detailed model set up can be found in the supplementary materials at the following link (https://osf.io/w7m25/). Consistent with our hypothesis, the results paralleled those we found with high control demand trials, with a significant twinness by parcel set interaction (p=0.0024), which we followed up with post-hoc contrasts.

Figure 9: Mean (and SEM) of Similarity Scores in High-Low Control Demand Contrast

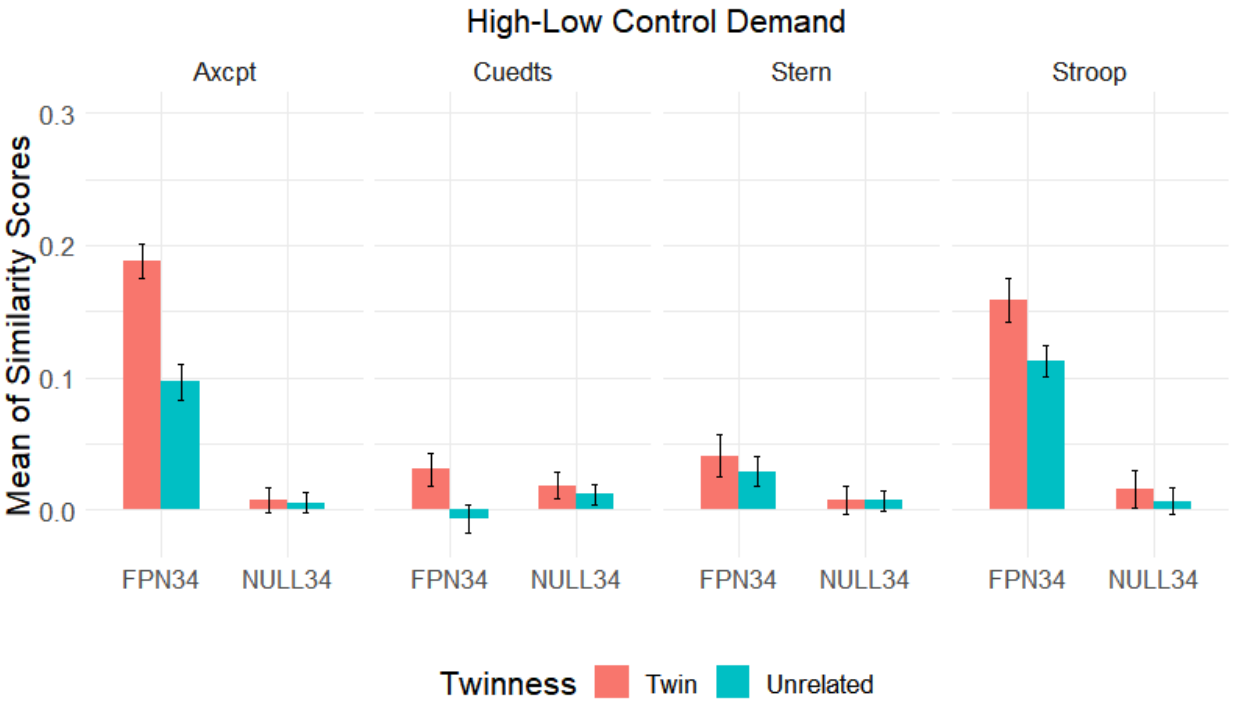


As predicted, we again observed a differential twin effect on the similarity scores in the two parcels. Importantly, the difference in similarity scores between twins and unrelated individuals in the high-low control contrast was significant for the FPN34 parcel set ($p_{corrected}<0.0001$) but not even close to significant for the NULL34 parcel set ($p_{corrected}=0.9231$). These results indicate that twins still exhibited greater pattern similarity than unrelated pairs, even when considering the neural activation difference between high and low control demand trials (see Figure 9).

Next, we computed the differences in pattern similarity within individual tasks (see Figure 10). The models for each task can be found in the supplementary materials at the following link (https://osf.io/ge4jw/). We detected a significant twinness by parcel set interaction in AX-CPT, and followed up with post-hoc contrasts. In AX-CPT, twins had significantly higher similarity in activation patterns than unrelated pairs in the FPN34 parcel set ($p_{corrected}<0.0001$) but not in the NULL34 parcel set ($p_{corrected}=0.997$). For the other three tasks, there was no significant

interaction. However, similar to what we did above, we built two linear mixed models for FPN34 and NULL34 in each of the three tasks to examine the direction of our hypothesis, that is, if twins were higher in pattern similarity than unrelated pairs in the FPN34 parcel set, but not the NULL34 parcel set. This hypothesis was again confirmed, in that we were able to detect significant differences in similarity scores for Cued-TS (p=0.0288) and Stroop (p=0.0237) in the FPN34 parcel set, but not in the NULL34 parcel set. For Sternberg, although the difference in pattern similarity was not significant for either of the two parcel sets, the general profile of the data was the same, with twins numerically higher than unrelated individuals in similarity scores, and the effect numerically larger in FPN34 than NULL34. Finally, because the magnitude of similarity scores were small in Cued-TS and Sternberg relative to the other two tasks, we conducted one-sample t-tests to confirm that the similarity scores of twins were significantly greater than zero for FPN34 in Cued-TS (p=0.009) and Sternberg (p=0.0086). Overall, even at the level of individual tasks, the twins exhibited greater similarity in activation patterns than unrelated individuals under increased cognitive control demand, an effect largely specific to the FPN34 parcel set.

Figure 10: Means of Similarity Scores of High-Low Control Demand Contrast by Tasks

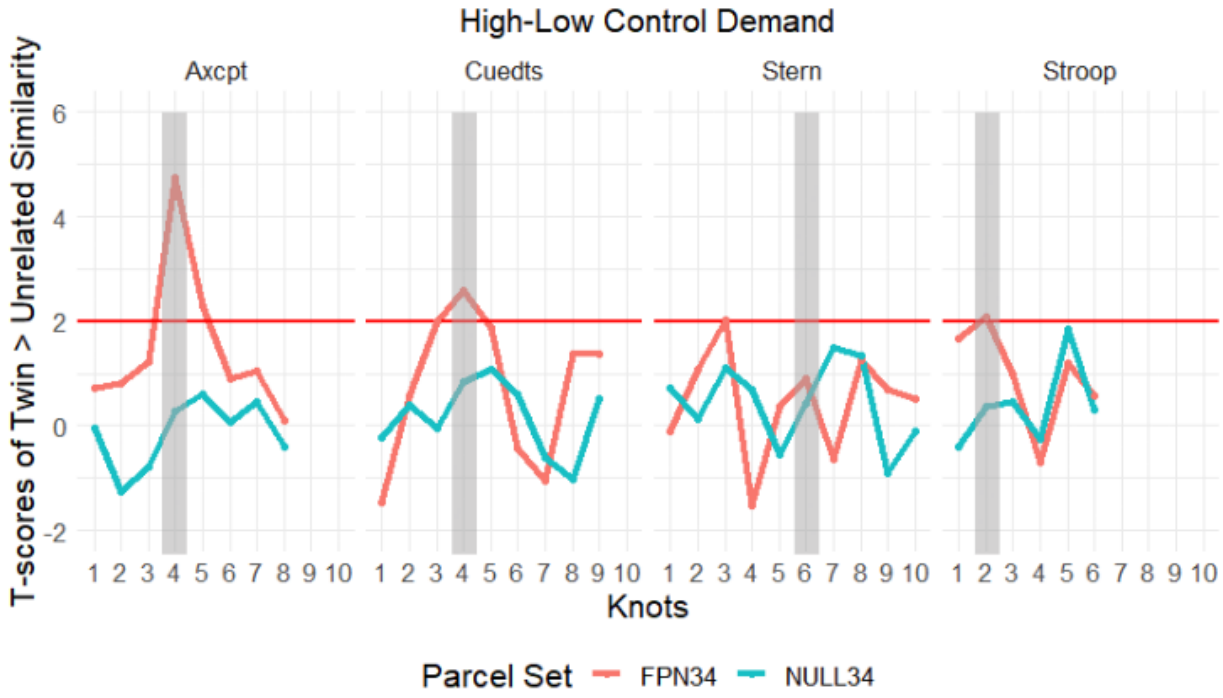


Temporal Dynamics of Twin Similarity: High-Low Control Demand.

Finally, we performed a robust two-sample t-test (two-tailed) to compare similarity scores of twins and unrelated pairs in the high-low control demand contrast at every timepoint. Again, even with this more stringent test, the difference in similarity scores between twins and unrelated pairs at the target timepoint were significant in three of the four tasks (not Sternberg). Critically, the twin effect also peaked at the target timepoint in the FPN34 parcel set for these same three tasks; whereas this temporal profile was not observed in the NULL34 parcel set (see Figure 11).

Moreover, in the NULL34 parcel set, there was no significant effect of twinness (i.e. twins > unrelated) at any timepoint.

Figure 11: Temporal Dynamics of Difference in Pattern Similarity (Twin > Unrelated) in High-Low Control Demand Contrast



A potential concern of comparing the NULL34 set with FPN34 is that we hand-selected the NULL34 parcels based on t-values from univariate analyses. Consequently, there could be potential biases introduced from the use of these parcels due to non-specific factors (e.g., low SNR). Therefore, we also ran the analyses with parcels from the somatomotor network (10819 voxels) as the control parcel set, since these are anatomically defined and pre-specified, and so unbiased with respect to our hypothesis. Results were very similar with this control parcel set: a significant twinness by parcel set interaction was observed in both high control trials (https://osf.io/x9p32/) and high-low demand contrast (https://osf.io/4bt6p/) at the target timepoint. For time-course analyses, the pattern similarity of the somatomotor network was very much like that of NULL34, in that it did not demonstrate specificity to increased control demand in any of the four tasks.

Discussion (1500 words maximum)

Understanding individual differences in cognitive control function is critical for both basic and translational research. The present work extends prior behavioral studies using multi-task, twin-based designs to examine cognitive control (Friedman et al., 2008; Miyake & Friedman, 2012) into the neuroimaging domain. Specifically, we utilized event-related fMRI combined with multivariate pattern analyses, to characterize neural activation patterns during multiple cognitive control tasks in both identical twin-pairs and pairs of unrelated individuals. The results provide the first evidence that twin similarity in the neural representation of cognitive control is largely domain-general, while also exhibiting both anatomic specificity to fronto-parietal regions and

temporal specificity to the time of highest control demand within task trials. Together, our findings suggest that the fMRI activation patterns indexing cognitive control can be considered akin to a 'neural fingerprint', reflecting the fine-grained systemic, yet idiosyncratic variation in neural activity within fronto-parietal regions that characterize individuals, and their genetically-identical twins. More generally, our work highlights the potential of twin-based neuroimaging investigations and multivariate pattern analysis approaches for exploring heritability questions within this domain.

Domain-generality of twin similarity

Current theoretical and empirical work has suggested a domain-general cognitive control capacity (Duncan, 2020; Kan et al., 2013; Miyake & Friedman, 2012), which enables flexible adaptation of thoughts and actions to fulfill a variety of task goals and demands (Cole et al., 2013; Braver, 2012). Yet this hypothesis could not be tested in prior studies using twin-based neuroimaging designs, since they relied on evaluating heritability of neural activation in single cognitive control tasks (Etzel et al., 2020; Koten et al., 2009; Matthews et al., 2007). Our work significantly extends these prior findings by demonstrating that twin similarity effects generalize across multiple cognitive control tasks; tasks which tap into different processes within this domain (e.g., selective attention, task-switching, working memory). In this regard, our neuroimaging design parallels that taken in prior behavioral studies, conducted in both adolescents (Friedman et al., 2008) and young adults (Friedman et al., 2016), in which multiple tasks tapping into cognitive control or executive functions are utilized (Friedman et al., 2008). However, the behavioral studies differ from the current work methodologically, in that they utilized latent variable methods to identify variation that is common to multiple tasks. Although we did not implement latent variable approaches here, this could be an important direction for future work; multivariate pattern similarity methods are quite flexible, and amenable to extensions that directly incorporate both cross-task and cross-twin similarity (cf. Etzel et al., 2020).

Anatomic specificity of twin similarity

Neuroimaging studies have consistently identified the frontal and parietal regions as involved in a wide range of cognitive control tasks, including but not limited to working memory, task-switching, and conflict resolution (Cole & Schneider, 2007; Cole et al., 2013; Dosenbach et al., 2006; Fedorenko et al., 2013; Hugdahl et al., 2015). Although most of this work comes from univariate activation and functional connectivity studies, a recent meta-analysis of MVPA studies indicated that the neural activation patterns within these regions are highly relevant for the encoding and representation of various task-relevant information (Woolgar et al., 2016). Our findings confirmed these fronto-parietal regions as a domain-general cognitive "core" (Duncan, 2010; Assem et al., 2020) engaged in all four cognitive control tasks. More importantly, we showed that twin similarity in neural activation patterns was specific to the FPN parcel set (including regions overlapped with the multiple-demand system shown in Assem et al., 2020), while being unreliable in the set of parcels selected based on an absence of cognitive control effects (from univariate analyses). It is important to note that although it could be argued that the NULL parcel set was unfairly biased in favor of our hypothesis due to this preselection, we also found similar specificity to the FPN when we compared to a somatomotor network that had been pre-defined based on anatomy and connectivity, rather than due to its activation profile in our cognitive control tasks.

The results also support prior work suggesting that fronto-parietal regions are a key locus of individual and genetic variation. Individual differences in higher cognitive processes and general fluid intelligence have been closely linked to variation in the neural activations and functional connectivity within the fronto-parietal regions (Cole et al., 2012; Duncan et al., 2020). In our own prior work (Etzel et al., 2020), we identified clear patterns of fronto-parietal genetic variation related to cognitive control, using a twin-based design and multivariate pattern similarity approach with the N-back task. Nevertheless, the current study departs from our prior one and from other neuroimaging work, in that those prior studies were able to directly estimate genetic heritability effects by incorporating dizygotic (fraternal) as well as monozygotic twins. In the current work, we chose to optimize our focus towards the demonstration of both domain-generality and task-specificity through the use of multiple tasks with temporally precise event-related designs. Yet the promising results of this somewhat smaller-scale study suggest the potential of extending the sample to include both dizygotic twins and related siblings, in order to better tease apart the underlying genetic and environmental contributions that underlie individual variation in the neural mechanisms of cognitive control. Furthermore, the identification of neural pattern similarity as a key marker of genetic influences within paired individuals opens up avenues for future research utilizing a longitudinal approach, to explore the effects of developmental or interventional effects on neural similarity among these pairs.

Temporal specificity of twin similarity

A key feature of our approach was the use of event-related task designs to probe cognitive control demands, which enable examination of the full timecourse of pattern similarity effects throughout the trial. To our knowledge this is the first time such an approach has been utilized in conjunction with a twin-based design, particularly across multiple tasks (cf. Koten et al., 2009). The results of the timecourse analyses provided further evidence of the specificity of twin-related similarity effects within fronto-parietal regions. In particular, the peak of the twin similarity effects was observed during the same time period of task trials in which cognitive control demand peaked (as observed from univariate task-activation profiles) for 3 of the 4 tasks. Moreover, this temporal specificity was only found in the FPN parcels. It is also important to note that although there may be a relationship between the time periods of peak activation intensity in brain regions and those when twin similarity effects are most prominent, this is unlikely to be due to methodological artifact or activation differences between the two groups. In particular, the mean activation timecourses of the twin and unrelated pairs were almost identical, indicating that the twin similarity effects were not a consequence of increased twin-related activation intensity effects. These timecourse analyses also suggest a departure from the interpretations of the one prior neuroimaging study to examine twin-effects related to task events and control manipulations (Koten et al., 2009; a study using working memory load and distraction manipulations). In that study, twin effects only partially overlapped with the anatomical locations and time periods exhibiting the strongest activation effects. One potential source of this discrepancy is that the sample size and number of twin pairs in the current study is much greater (n=94, 28 twin-pairs vs. n=30, 10 twin-pairs), potentially leading to more stability in the location and estimates. It is also possible that the discrepant profile of results was due to the differences in tasks and focus of the experimental manipulations, since the prior work examined working memory load effects, whereas the current study was optimized for examination of cognitive control demands.

The utility of the time-course analyses also suggests potential directions for future work. For example, although the peak of the twin similarity effects occurred during target or probe processing, some theoretical models predict temporal shifts in peak cognitive control utilization related to shifts in cognitive control mode. In particular, the Dual Mechanisms of Control framework (Braver, 2012) suggest a distinction between proactive and reactive modes of control. In the proactive control mode, control processes are hypothesized to be sustained and anticipatory, and so likely to be engaged and even strongest prior to target / probe onsets, such as during cue or delay periods in working memory tasks, and in cued tasks such as the AX-CPT and Cued-TS. Thus, one promising research direction would be to test whether twin similarity effects shift in terms of their temporal profile under conditions that encourage proactive control utilization. A strong hypothesis would be that shifts in the time-course of similarity effects in twin pairs would be predictive of a shift in behavioral markers indicating increased utilization of proactive control.

Conclusions

The current study is the first to utilize a multi-task, event-related fMRI twin-based design to systematically examine neural activation patterns related to cognitive control demands in terms of both individual variability and potentially heritable similarity effects. By leveraging our theoretically-guided task battery of cognitive control, we were able to provide promising evidence that genetic influences partly contribute to individual differences in the neural representation of cognitive control processes. The approach leveraged here, defining twin-similarity effects in terms of multivariate neural activation patterns, highlights the fine-grained nuances of cognitive control variation occurring at the level of neural activation patterns. Critically, this variation demonstrates both anatomical and temporal specificity, yet generalizability across different experimental assays of cognitive control function. In this regard, our findings offer both new insights and targets for basic and translational research aimed at understanding the neural mechanisms that give rise to individual differences in cognitive control function.

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