The WU-Minn HCP Lifespan Pilot Project
Preliminary Report
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Executive Summary: Based on the encouraging early success of the Human Connectome Project (HCP), NIH in the fall of 2013 awarded supplements to the WU-Minn and MGH/USC consortia to explore the feasibility of extending the HCP methods to examine brain circuits across the human lifespan. The data being generated as part of the HCP are extremely high quality, and include anatomical, diffusion and both resting state and task based functional MRI. However, the HCP acquisition protocol for the imaging data alone is 4+ hours. This has proven to be routinely feasible for healthy young adults, but it is problematic for children, older adults and other special populations to cope with scan sessions of that duration. Thus, a major goal of the HCP Lifespan Pilot supplement has been to develop and evaluate a shorter protocol that is tolerable and realistic across the human lifespan, while still providing HCP-style data of as high a quality as possible. This report summarizes our initial success using a modified acquisition protocol of ~2 hr total duration that as of mid-January, 2015, has been carried out on 83 subjects on the WashU 3T Siemens Skyra Connectom scanner, 75 subjects on the UMinn 3T Siemens Prisma scanner, and 51 subjects on the UMinn Siemens 7T scanner. Our preliminary analyses of the data acquired on the WashU 3T scanner support four main conclusions: 1) The 2-hour "Lifespan HCP" protocol provides excellent quality data for assessing brain structure, connectivity and function, similar in quality to that generated by the main HCP protocol; 2) the duration of the Lifespan HCP protocol is well tolerated by the majority of participants, even in the younger (e.g., 8-9) and older (65-75) age groups; 3) the youngest and oldest age groups have a higher incidence of individuals with unusable or lower quality data (mostly due to movement), suggesting that a large-scale Lifespan project should plan to oversample in these ages to ensure adequate sample sizes with high quality data in all age groups; and 4) analyses within each age group indicate that we see neurobiologically appropriate patterns of brain activation and connectivity within each age group, as well as preliminary evidence suggesting interesting age-related differences.

Introduction. The WU-Minn HCP consortium is currently in its final year of acquiring, analyzing, and sharing extensive neuroimaging and behavioral data from a target number of 1200 healthy adults. The participants spend two full days at Washington University, where they undergo a total of 4 hours of scanning (structural MRI, diffusion MRI, task fMRI, and resting-state fMRI) plus several hours of behavioral data acquisition. A subset of 200 participants will also be scanned on the 7T scanner at CMRR in Minnesota; about half of the target 200 subjects have been scanned to date. Optimized preprocessing pipelines and advanced analysis methods have been implemented to capitalize on the outstandingly high quality of the HCP data. Data sharing by way of the ConnectomeDB database has enabled thousands of investigators to make use of this exceptional resource.

For the HCP Lifespan Pilot project, we are studying six age groups (4-6, 8-9, 14-15, 25-35, 45-55, and 65-75). During initial piloting, we determined that a scan protocol lasting 2 hours (1 hr/day) was well tolerated by participants in the five older age groups (8-9yr and above). For the youngest group (4-6yr), we determined that they would tolerate only a shorter overall scan duration. Also, their smaller head size mandated a customized head coil (see below). Hence, the cross-age comparisons that include this youngest group will need to take these major differences into account.

All age groups are being scanned on the WashU ("WUSTL") 3T scanner, which has a maximum gradient strength of 100 mT/m. A separate set of participants (8-9yr and older) is being scanned at UMinn ("MINN") on both the 3T Prisma and 7T scanners. The Prisma scanner has a maximum gradient strength of 80 mT/m, twice that of a standard 3T Trio and approaching that of the Skyra Connectom scanner. Data collection and analysis are still underway for the Lifespan Pilot on all three scanners. Here, we provide preliminary results and analyses from the WUSTL scanner for the 8-9yr and older age groups. Our findings indicate that modified HCP-style data acquisition and analysis can be successfully carried out across a wide range of age groups.

Study Design, Acceptability and Compliance

Figure 1: HCP WUSTL Lifespan Protocol Overview

DAY 1	DAY 2	Scan Protocols		

DAY 1

Consent, Intake, Review of Exclusion, & Substance Screen (30 minutes)

Mock Scanning (20 minutes)

Break & Snack (5-10 minutes)

Scan Session #1 (60 minutes)

Break & Snack (5-10 minutes)

Behavioral #1 NIH Toolbox (45-90 minutes depending on age)

DAY 2

Scan Session #2 (60minutes)

Break & Snack (5-10 minutes)

Behavioral #2 HCP Non-Toolbox (30-60 minutes depending on age)

Break & Snack (5 to 10minutes)

Scan Session #3 *Ages 4-6, 8-9, 65-75* (30-45 minutes)

Exit Interview (20 minutes)

Scan Protocols

4-6 children

Session A
rfMRI P1   6 m
T1w   7 m
T2w   6 m
rfMRI P2   6 m
Emotion Mod 6 m
  Total   35 m

Session B
rfMRI P3   6 m
dMRI P1   10 m
dMRI P2   11 m
rfMRI P4   6 m
Social Cog   7 m
  Total   44 m

Session C
rfMRI P5   6 m
T1w_vNav   10 m
T2w   6 m
Gambling Mod 8 m
  Total   33 m

8-9 children, 65-75 adults

Session A
rfMRI P1   10 m
T1w   7 m
T2w   6 m
rfMRI P2   10 m
Nback   10 m
Emotion   5 m
  Total   52 m

Session B
rfMRI P3   10 m
dMRI P1   10 m
dMRI P2   11 m
rfMRI P4   10 m
Social Cog   7 m
Gambling   6 m
  Total   59 m

Session C
rfMRI P5   10 m
T1w_vNav   10 m
T2w   6 m
rfMRI P6   10 m
  Total   40 m

14-15 teens, 25-35 adults, 45-55 adults

Session A
rfMRI P1   10 m
T1w   7 m
T2w   6 m
rfMRI P2   10 m
Nback   10 m
Emotion   5 m
T1w_vNAV   10 m
  Total   62 m

Session B
rfMRI P3   10 m
dMRI P1   10 m
dMRI P2   11 m
rfMRI P4   10 m
Social Cog   7 m
Gambling   6 m
  Total   59 m

The Lifespan HCP protocol, like the main HCP protocol, is spread across two days for both WUSTL and MINN. The flow for each day for WUSTL is shown in **Figure 1**, as is an overview of the scan protocols. On day one, participants come for the intake interview, mock scanning, a first imaging session and a first behavioral session. On day two, participants return for a second imaging session and a second behavioral session. The children (4-6 and 8-9) and older adults (65-75) also do a third short scan session.

The HCP Lifespan protocol was designed to acquire high quality data, as the main HCP protocol, but with shorter total scan time. In brief, this includes structural MRI (T1w, T2w) at 0.8mm voxel size (vs. 0.7mm in the main HCP; 20 minutes of diffusion MRI (dMRI) instead of 60 minutes; 40 minutes of resting state fMRI (eight 5-minute scans) instead of 60 minutes (four 15-minute scans); and four fMRI task scans, instead of the seven acquired in the main HCP. When scheduling permits, we also acquire a third scan session in children and older adults. Its main purpose is to evaluate a new navigator-guided T1w scan protocol ("T1w_vNav" in Fig. 1) developed by MGH that detects and compensates for head movements in real-time. It offers the prospect of significantly improved structural data quality, especially for age groups having a higher incidence of head movement, but needs critical evaluation (see below). At MINN, locally-recruited participants do only the intake and the scanning sessions, with each participant scanned on the PRISMA on one day and on the 7T on a separate day. To reduce the burden on participants, the structural scanning only occurs on the PRISMA and only resting state and diffusion data are collected.

Table 1 summarizes our recruitment and scanning progress at both WUSTL and MINN. Overall, all age ranges have tolerated the scanning sessions well (~1 hour per session), and only a few participants failed to complete the protocols at either WUSTL or MINN. Not surprisingly, the 8-9 year old children have somewhat greater difficulty than the teenagers and the older adults.

Table 1: Subject Recruitment Outline for HCP Lifespan								
WUSTL SKYRA			**MINN PRISMA**			**MINN 7T**		
Complete or in progress	To be Scheduled	Did not complete*	Complete or in progress	To be Scheduled	Did not complete*	Complete or in progress	To be Scheduled	Did not complete*

4-6	Have completed several rounds of pilot testing with new head coil			NA	NA	NA	NA	NA	NA
8-9	25	0	3	8	12	3	6	14	0
14-15	11	14	1	9	12	1	8	12	0
25-35	24	1	0	20	0	0	17	3	0
45-55	23	2	1	20	0	3	10	10	1
65-75	20	4	0	23	1	1	13	7	%

* Incomplete scans reflect excessive movement or a participant's inability to tolerate the scans.

Behavioral Data

The Lifespan Pilot behavioral data is acquired across two sessions on separate days (see Appendix Figs. 3 & 4 for details). The tasks and session durations are well tolerated by all age ranges, consistent with the fact that both NIH Toolbox and non-Toolbox measures were designed for use across a wide age range. We find expected age-related effects in all domains, including personality. For example, **Figure 2** shows unadjusted (blue) and adjusted (purple) scores from the Total Cognition Measure (an aggregate across individual NIH Toolbox cognitive tasks). There is a significant main effect of age ($p<.001$) in the unadjusted scores, but not in the adjusted scores. Data for the other tasks in the NIH Toolbox and the non-toolbox behavioral session are shown in *Appendix Figures 6-19* (Toolbox) and *Appendix Figures 21-24* (non-Toolbox).

Figure 2: NIH Toolbox Total Cognition Scores
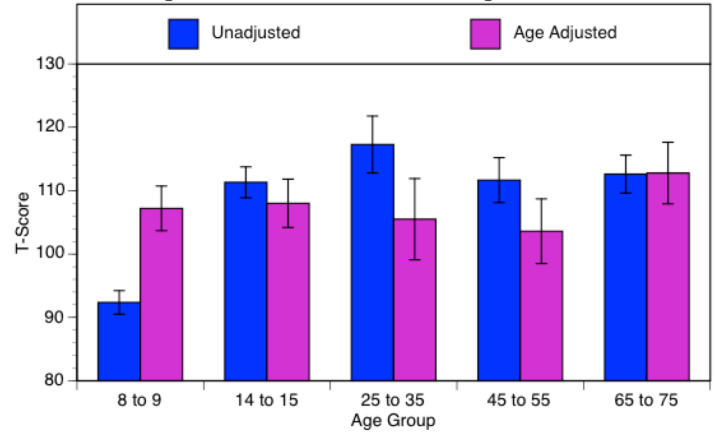
Structural Images

The Lifespan-HCP protocol acquires T1w (MPRAGE) and T2w (SPACE) structural images at a resolution of 0.8mm isotropic voxels - substantially higher resolution than conventional 1mm voxels and close to the 0.7mm voxels acquired in the main HCP. This reduces scan time (~13min vs 16min) while enabling the generation of high-quality cortical surface models and also myelin maps (based on the T1w/T2w ratio) that are informative about functional organization in individual subjects. This is supported by Figure 3, which shows the similarity of myelin maps from four Lifespan-HCP subjects (**Figure 3, left**) with those in four main-HCP subjects (**Figure 3, right**), including heavily myelinated regions (red, yellow) in primary somatosensory, auditory, and visual cortex, retrosplenial cortex and area MT (arrows).

Figure 3: Similarity of Myelin Maps from Lifespan-HCP and main-HCP as Index of T1/T2 Quality

Lifespan-HCP myelin maps
(four 25-35 year olds; 0.8 mm isotropic T1w, T2w)

Main-HCP myelin maps
(four 25-35 year olds; 0.7 mm isotropic T1w, T2w)
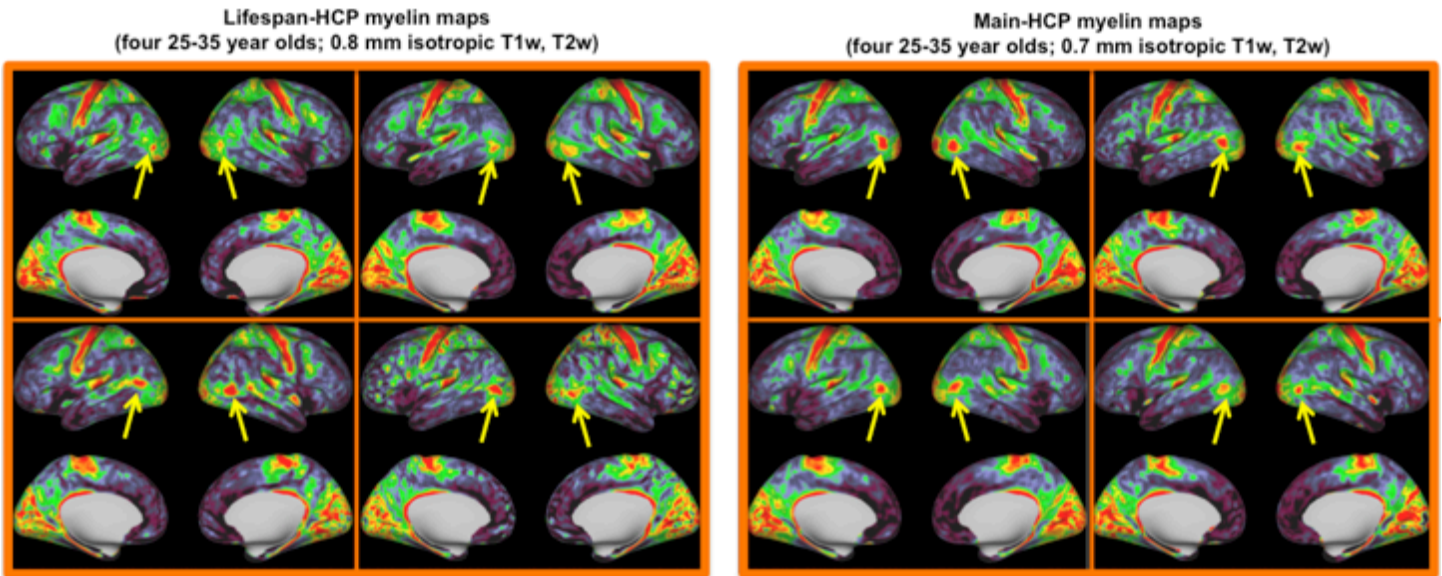
Overall the structural MRI data quality is high to very high across all Lifespan-HCP age groups, as judged by the same QC expert who has evaluated all main-HCP structural images. The average highest quality scan rating for each age group is shown in *Appendix Slide 26*. As would be expected, there is a significant effect of age, with scan ratings higher for the 25-35 year old adults than the 8-9, 45-55 or 65-75 year old (trend) participants. The appendix also shows an example surface generated for a participant from each age group (*Appendix Slides 28-32*). *Appendix Slides 33 and 34* show that we see linear and quadratic effects of age for both gray and white matter volume in the T1 acquisitions, as expected from published studies (e.g., a peak in whole brain cortical gray matter in middle childhood with a decline across the rest of the life span; an inverted U-shape curve for white matter volume with a peak in mid adulthood).

As noted above, in many subjects we acquire a T1 Navigator guided acquisition developed at MGH [1] in addition to a standard T1w scan. This Navigator guided sequence is designed to prospectively correct for motion by reacquiring echoes in k-space whenever motion is detected. It requires a longer inversion time (TI), which may reduce gray/white contrast. Our preliminary analysis suggests there may be some benefit in the 8-9 year old children (~0.5 point difference on a four-point rating scale), whereas for other age groups we have yet to see a systematic improvement in image quality ratings for the T1Nav acquisitions. We will continue making these comparisons in the remaining scans, including the 4-6 year old age group.

Diffusion Imaging

The main HCP diffusion protocol (six 10 minute blocks, 1.25mm voxel size) benefits from the ability of healthy young adults to hold still for an hour-long session, thereby yielding exquisitely detailed structural connectivity maps of the brain. This duration is challenging for children and older adults (and also individuals with clinical disorders), and we decided that 20 minutes was a practical limit for diffusion acquisition in the context of the Lifespan-HCP protocol. We carried out pilot protocols and settled on a modified 20 minute dMRI protocol that provides excellent data quality based on metrics derived from FSL tractography tools (e.g., orientation uncertainty, detection of crossing fibers, and SNR/CNR). It entails four runs (each 5 min), a multiband factor of 3, TR=3700 ms, TE=75 ms, and 1.5 mm isotropic voxels. For the shorter (20min) duration, piloting indicated that the Lifespan voxel size of 1.5mm is better than the 1.25mm voxel size that is feasible with the hour-long main HCP protocol. Each dMRI run includes 75 diffusion weighting directions and 2 shells of b=1500 and 3000 s/mm, each sampled on the whole sphere, plus 5 interspersed "b=0" acquisitions. Diffusion weighting is applied using monopolar diffusion encoding gradients, which minimizes TE, and thereby increases SNR. The dMRI scans are acquired in pairs with opposing "R>L" and "L>R" phase encoding polarity, which increases SNR and allows corrections of susceptibility-induced and eddy-current induced distortions using recent HCP

developments and pipelines.

Figure 4: Comparison of main HCP, HCP-Lifespan and WhiteHall Diffusion Acquisitions
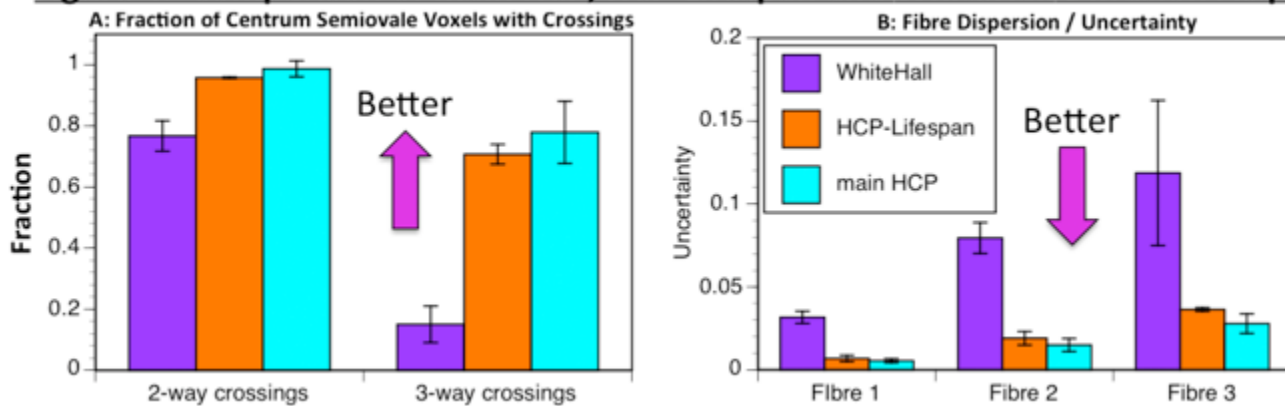
Figure 4 shows that by two objective measures applied to four participants from each of three imaging protocols, the quality of Lifespan-HCP dMRI data approaches that of the main-HCP data and is markedly better than obtained using a conventional protocol (10 min duration, 2mm voxel size) used in the large WhiteHall population study [2]. Specifically, **Figure 4A** shows that both the main-HCP data (blue) and Lifespan-HCP data (orange) outperform WhiteHall data (purple) in terms of the incidence of 2-way fiber crossings (left histogram) and 3-way fiber crossings (right histogram) in the centrum semiovale (a region with high fiber complexity). **Figure 4b** shows that both the main-HCP and the Lifespan-HCP data more reliably estimate fiber orientations (lower values of fiber dispersion and uncertainty) than does the WhiteHall data. These observations indicates that both HCP datasets have higher sensitivity to and better resolution of crossing fibers, which is critical for accurate tractography. Additional evidence buttressing this conclusion are included in *Appendix Figure 36* (higher spatial resolution of the HCP data) and *Appendix Figures 37 & 38* (exemplar probabilistic fiber tracking for the three protocols). Altogether, these preliminary findings indicate that the Lifespan-HCP diffusion data are much higher in quality than from conventional protocols and approaching that of the main HCP despite the shorter scan duration (20 vs 60 min).

In a preliminary analysis of age-related differences, we focused on fractional anisotropy (FA) and mean diffusivity (MD), which are known to vary non-linearly across the lifespan. We applied FSL's Tract-Based Spatial Statistics (TBSS) to the whole-brain white matter skeleton, including an optimized registration protocol that makes use of intermediate age-specific FA templates to account for the wide age range of the participants. We also investigated FA and MD values in 10 major fiber tracts in each hemisphere (reconstructed using probabilistic tractography) using the Lifespan Phase 1A dataset (n=26). **Figure 5** shows that estimated FA values in each major white matter tract vary across the lifespan in an inverted U-shaped curve, consistent with previous studies. Not all tracts peak at the same age: the data suggest that several association tracts, including the cingulum bundle, anterior thalamic radiations (for MD), and uncinate fasciculus, peak at later ages, whereas the motor-related corticospinal tract (for FA) and superior thalamic radiations (for MD) peak at earlier ages. *Appendix Figure 39* shows analogous results for MD.

Figure 5: FA Values in Major White Matter Tracts Across the Lifespan
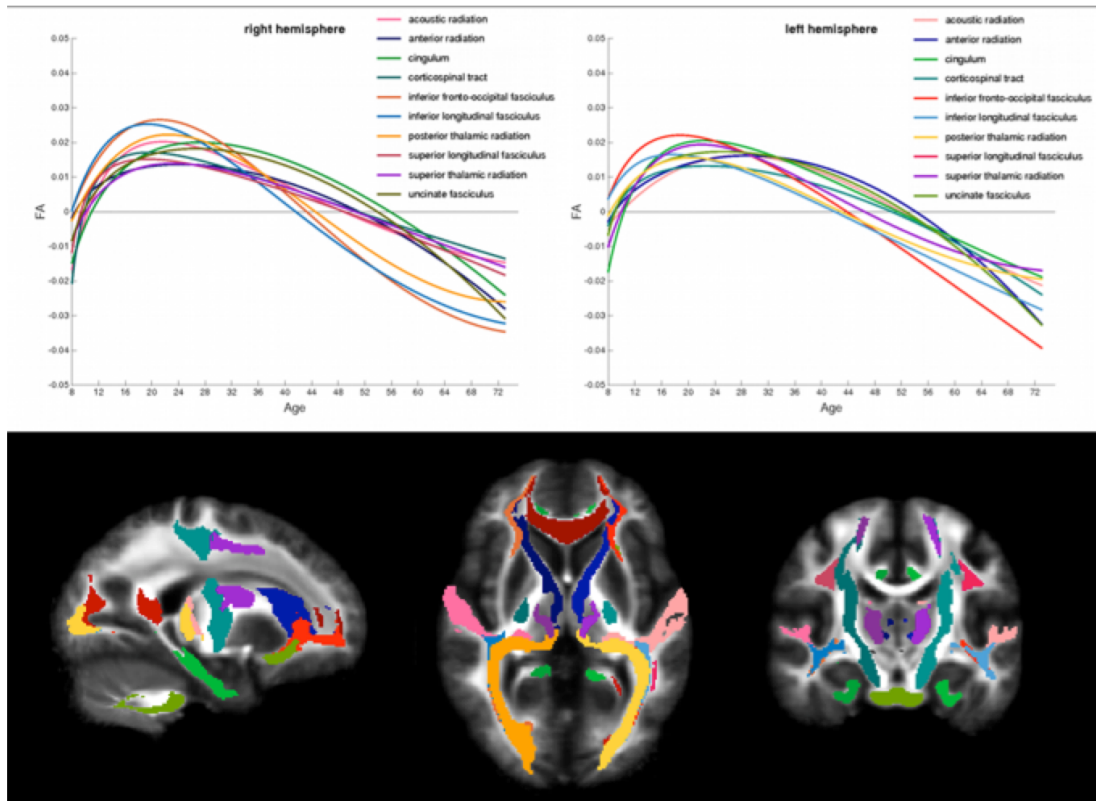
Note: In each tract virtually reconstructed using probabilistic tractography, the same qualitative fits modelled well the average FA and MD lifespan trajectories. These (inverted) U curves showed varying peaks for each tract across the lifespan, with the cingulum bundle, the anterior thalamic radiations and the uncinate peaking the latest and the corticospinal tract earliest for FA .

Resting state fMRI

For resting-state fMRI (rfMRI), the Lifespan-HCP acquires four 5-minute scans (eyes-open loose-fixation) on each of two days (40 min total). The shorter overall duration (40 vs 60 min) and shorter individual scans (5 vs 15 min) compared the main HCP reflects practical constraints in achieving good compliance across a wide age range. The decision to use shorter (5 min) acquisitions for the Lifespan-HCP is supported by *Appendix Slide 41,* insofar as average head movement increases progressively during the continuous 15-minute acquisition for main HCP but with less of an increase during the 5-minute acquisitions for the Lifespan-HCP.

We also compared the reliability (day 1 vs day 2) of metrics obtained using all data from the main HCP (30 minutes per day) compared to the first 20 minutes of each day (equivalent to the Lifespan-HCP). The test-retest reliability (ICC) for average connectivity within each of a set of a priori networks was almost identical for the Lifespan-HCP duration (MEAN across networks = 0.61, range .45 to .67) as compared to the main HCP (MEAN across networks = .61, range = 0.46 to 0.71). We also compared the similarity of the connectivity metrics for the main HCP to the amount of data equivalent to the Lifespan-HCP in subjects from the main HCP. The connectivity metrics were almost identical *(eta* value [range 0-1] of .99 for the similarity of the matrices). For these reasons, we believe the Lifespan-HCP protocol can generate data of similar high quality to the main HCP, and that it provides detailed and reliable maps of connectivity in core brain networks in individual subjects, and which is feasible for obtaining high quality data in children and older adults.

A critical initial issue in analyzing Lifespan rfMRI data is to assess head movements at different ages, because movement affects estimates of functional connectivity. **Figure 6** shows, as expected, that average head movement varies with age and is highest in 8-9 year old children (see also *Appendix Figure 42*). Importantly, there is considerable intersubject variability in each age range, and there are enough subjects wth low movement at all ages to enable a 'motion-matched' set of comparisons (see cut off line in **Figure 6**). In a full Lifespan project, it would be advisable to oversample participants in age groups likely to have high movement. The remaining analyses described used only the participants below the cut off line shown in **Figure 6**.
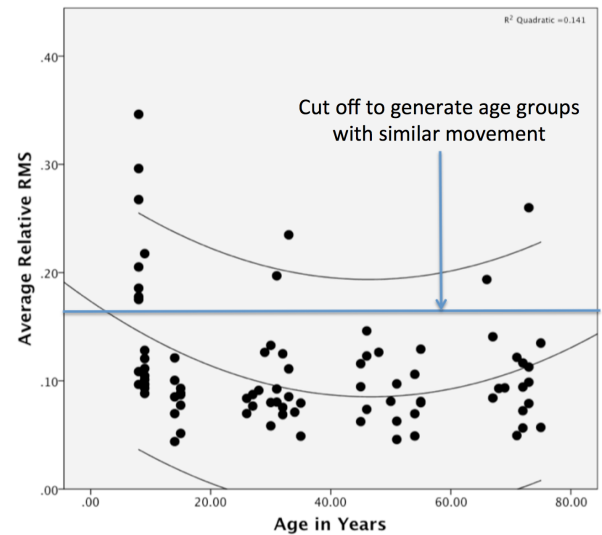

Figure 6: Movement in Resting State Data

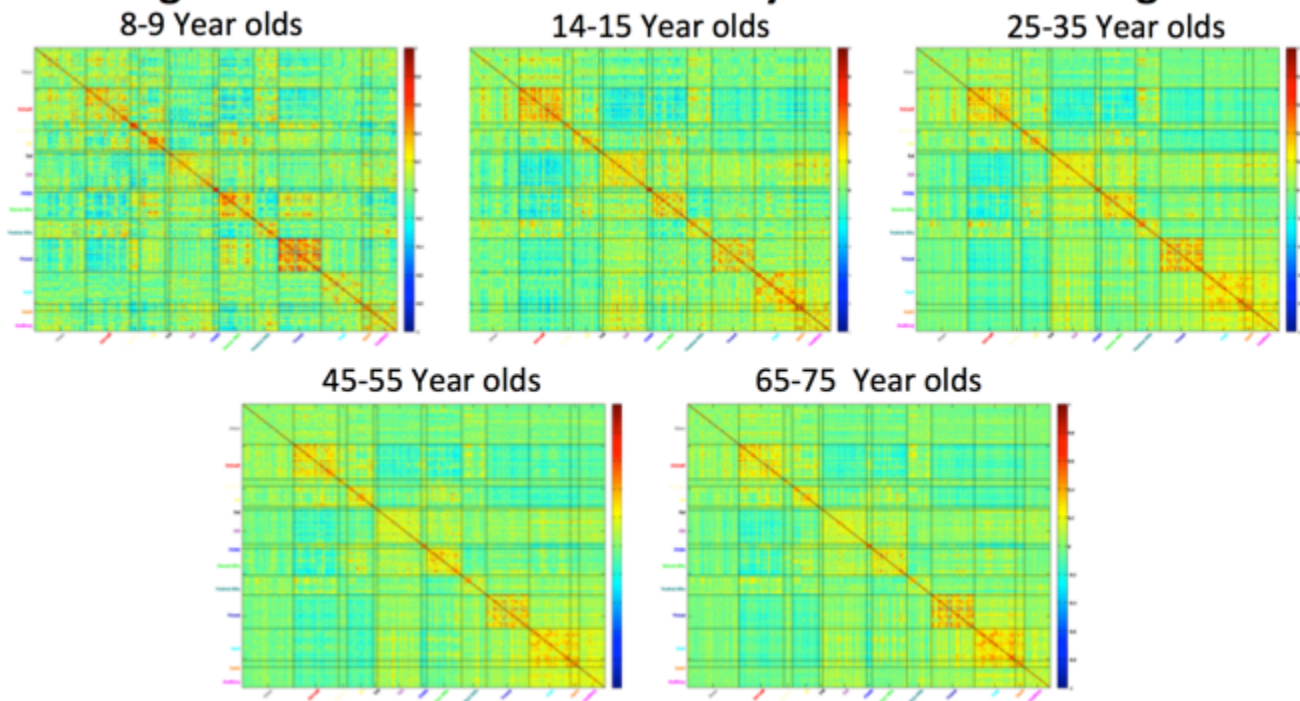Figure 7: Parcel-Wise Connectivity Matrices within Age
8-9 Year olds   14-15 Year olds   25-35 Year olds
45-55 Year olds   65-75 Year olds

Figure 7 compares group-average parcellated connectivity matrix across age groups, using a published *a priori* parcellation scheme [3] applied to the functional connectivity data. The functional connectivity pattern in young adults is similar to published reports. The connectivity matrices for different ages are similar but not identical. We also analyzed network-wise connectivity matrices (e.g., average connectivity within all nodes/parcels belonging to the Default Mode Network, and between the Default Mode Network and the Frontal Parietal Network) and found patterns that are similar but not identical across age groups (*Appendix Slide 43*). We examined age effects both in a "parcel-wise" analysis of connections between all parcels in our *a priori* parcellation [3] and based on average connectivity within each network. We identified encouraging trends, such as an age-related difference in connectivity within Auditory network regions (Fig. 8A) and a different pattern between Auditory and somatosensory networks (Fig. 8B) *Appendix Figures 44-47* show additional illustrations of possible age-related differences in connectivity. However, we stress that it is premature to draw strong conclusions about age-related differences in functional connectivity, given the modest sample sizes analyzed to date.

Figure 8: Auditory Network Connectivity
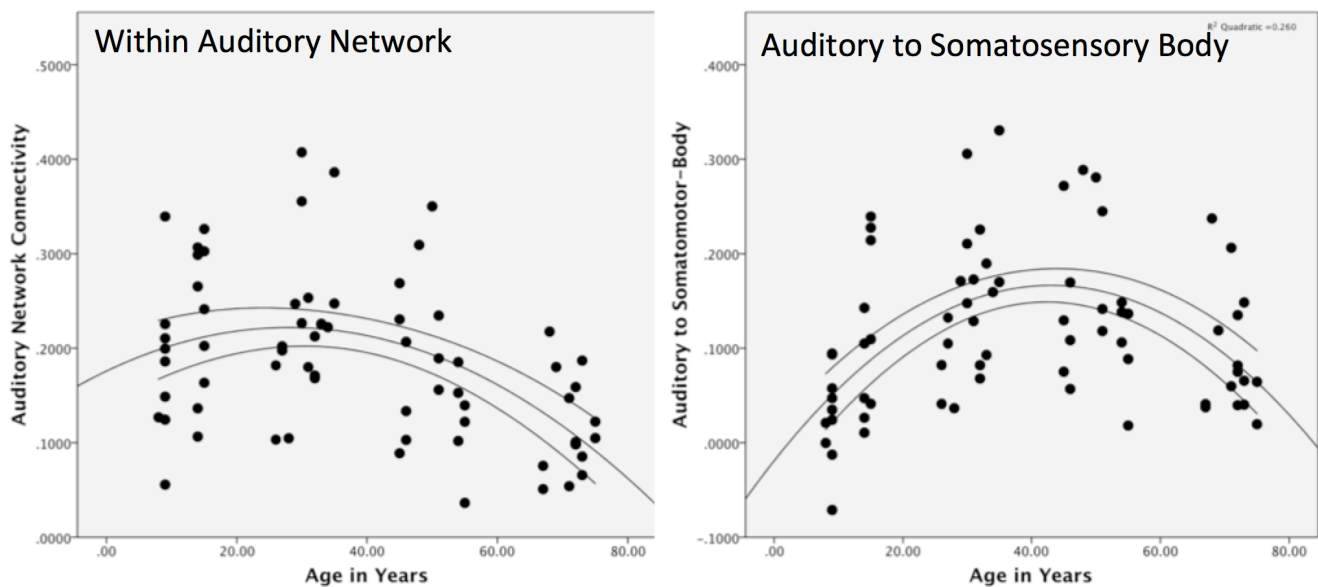
Task fMRI (tfMRI): The Lifespan HCP protocol includes four of the seven tasks from the main HCP, with the smaller number respecting the time constraints and subject burden for younger children and older adults. Specifically, we chose Working Memory (2-Back vs. 0-back), Emotion (Fear Face vs Shape, Gambling (Reward and Loss) and Social Cognition (Mental Interactions vs Random Interactions) [4], because they tap constructs and neural systems most relevant to understanding age related differences in neural networks associated with different cognitive, affective and social functions. Each task is run exactly as in the main HCP, except that the Working Memory task used for Lifespan-HCP was simplified to include only faces and places as stimulus types instead of faces, places, body parts and tools as used in the main HCP. Once scanning commences on the youngest children (4-6 yr), we will further simplify the response options, based on our experience with imaging children in this age range. Preliminary analyses demonstrate robust patterns of activation within each age group, as illustrated for the Emotion task in **Figure 9** and for the other three tasks in *Appendix Figures 49-51*. To begin exploring age-related effects, we conducted analyses based on (i) whole brain voxel-wise comparisons, (ii) the Gordon et al. networks [3] described above, and (iii) ROIs derived from analyses of each of the same tasks in the main HCP data. Not surprisingly, the voxel-wise whole brain analysis revealed few age-related effects, reflecting the stringency of multiple comparison corrections combined with modest sample sizes. Both the Gordon parcel and the main-HCP ROI based analyses provide suggesting evidence for age-related differences. For example, **Figure 10** illustrates age-related differences in ROIs within both the Salience network and the Ventral Attention Network in the Gambling task contrast of Reward versus baseline. *Appendix Figure 52* illustrates age-related differences in Frontal Parietal Network activity during Social Cognition.
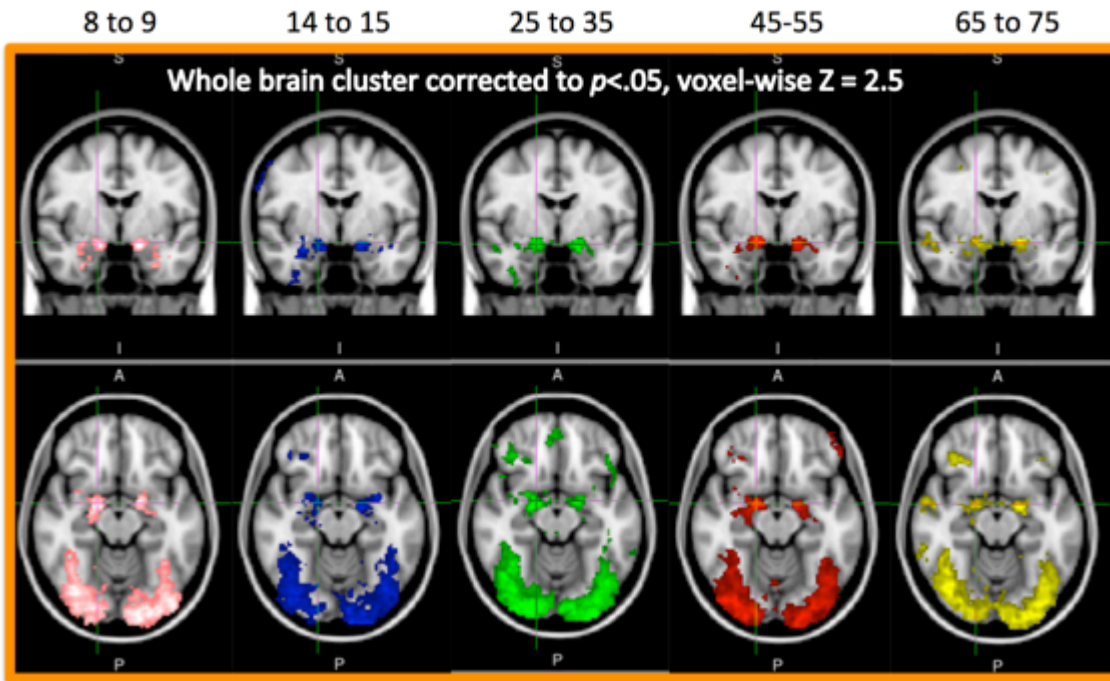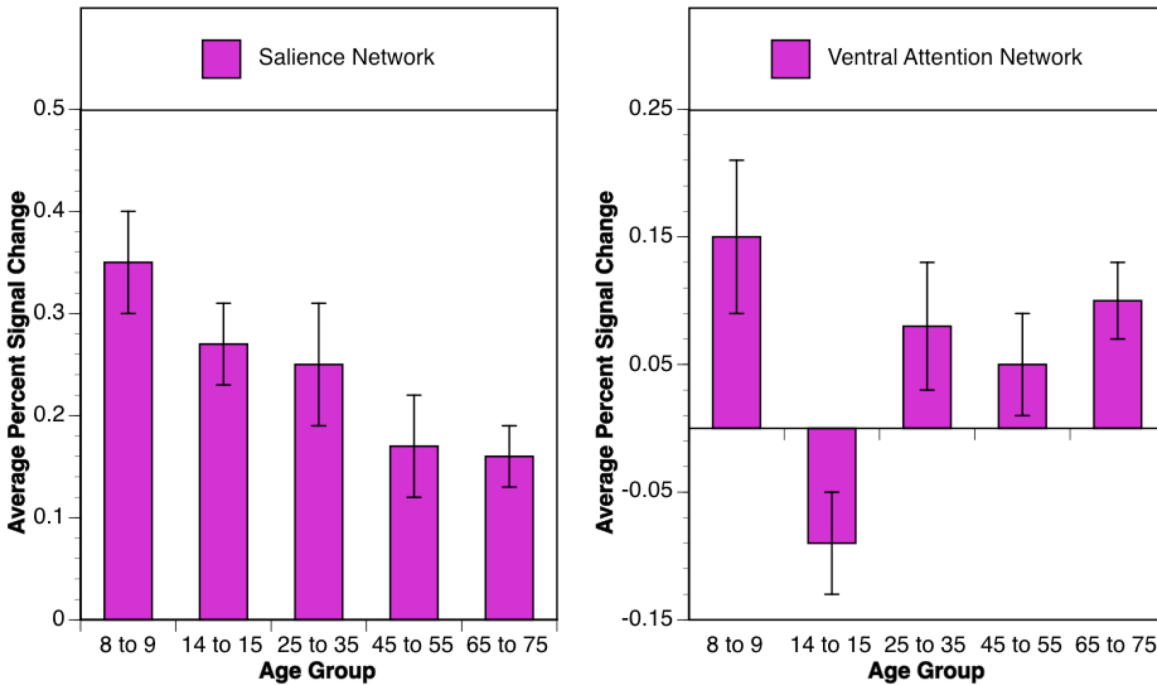
Figure 9: Whole Brain Voxel-Wise – Emotion Task

Figure 10: Age Related Differences During Gambling

Concluding Comments.

In general, our consortium members are pleased by the high quality of the HCP Lifespan Pilot data for each of the MRI modalities. It is encouraging that a number of our preliminary analyses provide strong suggestions of age-related differences in brain structure, function, and connectivity, even though the data collection phase is still underway and the sample sizes are modest.

Many additional analyses will be of interest to carry out on the Lifespan HCP datasets. This includes further analyses to assess whether any age-related differences are confounded by movement differences between age groups. Of particular interest will be analyses of the 3T Prisma and 7T datasets acquired at UMinn. For diffusion imaging, it will be important to determine whether 20min of scanning on the 3T Prisma (80 mT/m maximum gradient strength) provides comparable data quality to that on the Skyra Connectom scanner (100 mT/m maximum gradient strength). We will soon be launching the HCP preprocessing pipelines on the Prisma and 7T data, which will enable analyses and comparisons similar to those described herein for the WUSTL 3T data.

References
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