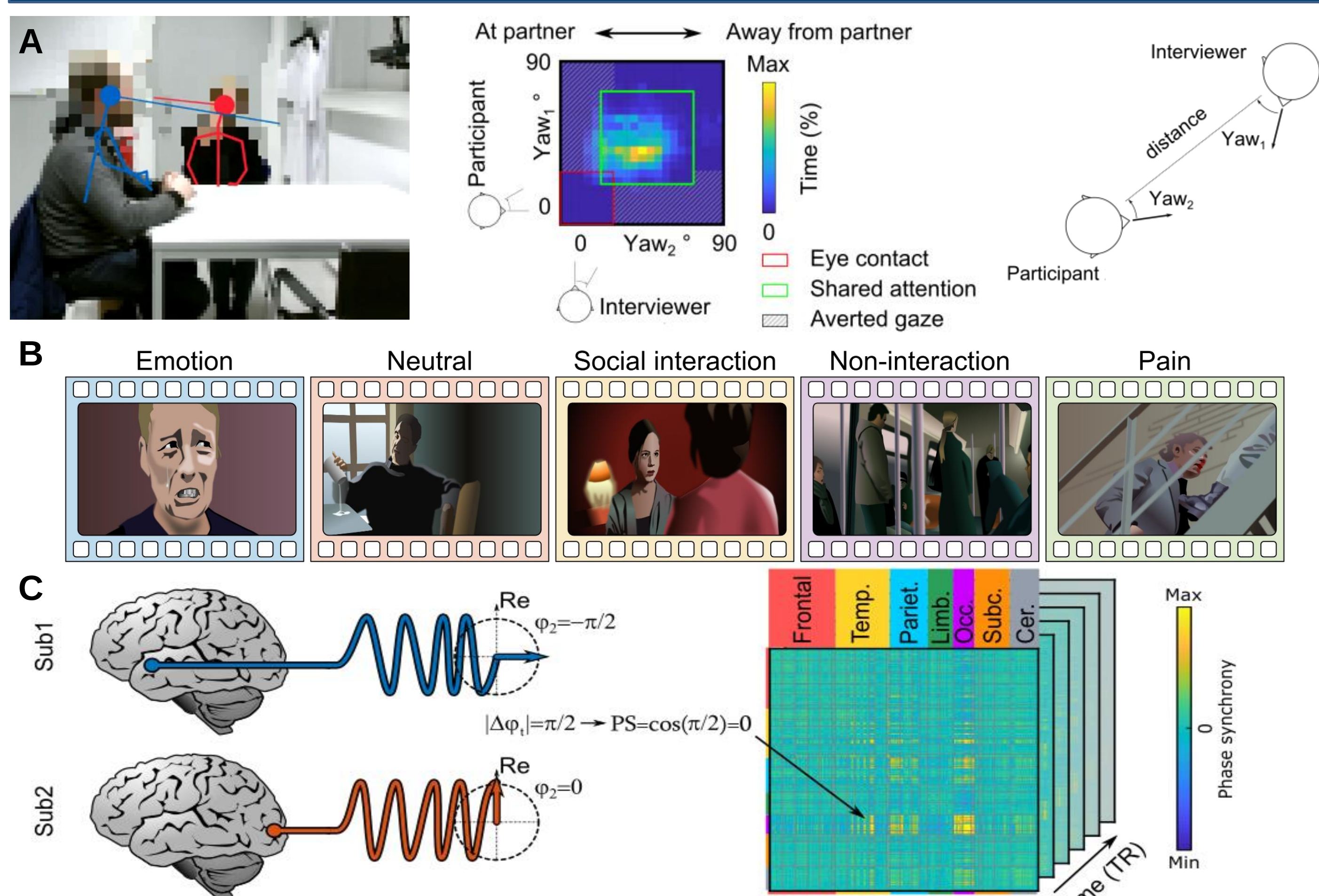


Introduction

Autism spectrum disorder (ASD) is a developmental disorder marked by impaired social interaction and stereotyped behaviors. However, characterization of these symptoms generally relies on subjective and categorical measures that lack specificity. Moreover, fMRI studies rarely employ paradigms that directly assess social functioning and, thus, it remains unclear whether the findings are relevant for the social functioning of the participants, or whether they relate to more general group differences.

Here, we measured unconstrained social behavior during real-life dyadic interaction during an interview, by means of motion tracking. During a subsequent fMRI session, we measured brain responses during perception of socio-emotional events in short movies to link the within-subject behavioral and neural signatures of ASD. We expected that patients would exhibit aberrant interpersonal orienting behavior and that their brain activity patterns would be less correlated between subjects compared with neurotypical (NT) controls. Our main question was whether the idiosyncrasy of brain activity in the ASD group was related to idiosyncratic social behavior.

Methods

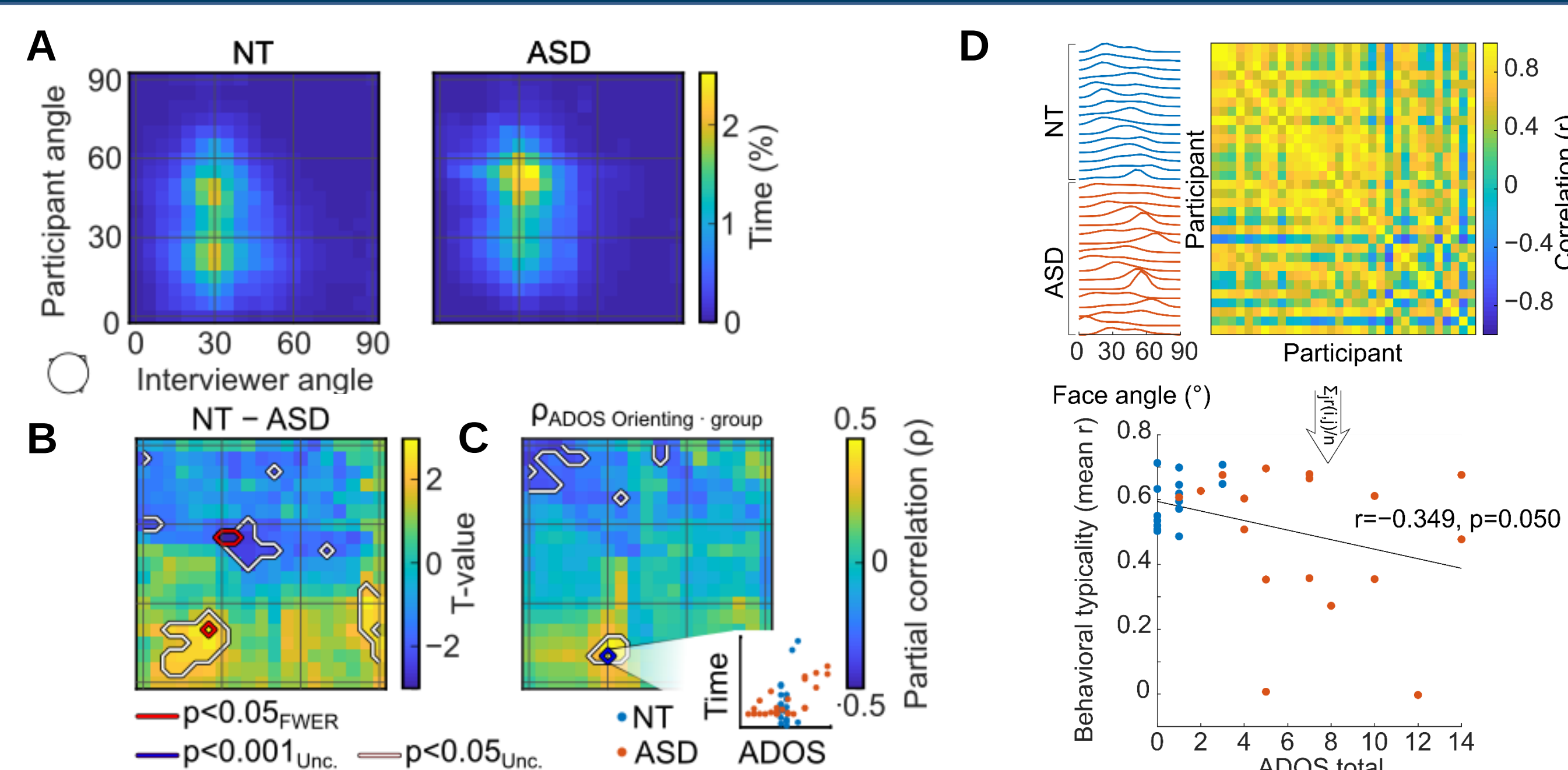


A Social orienting behavior was measured during ADOS-2 interview with skeleton tracking of Kinect V2 (25 ASD, 19 neurotypical; NT). Orientation of face in relation to the direction of the interaction partner was calculated for participant and interviewer and 2-dimensional joint orienting histograms were constructed. The colors correspond to the total percentage of time the pair spent at each joint orientation that are also indicative of gaze behaviors (e.g. joint low angles predict eye contact).

B During fMRI, 52 previously validated^[1,2,3] short (9–22s) clips of Hollywood movies depicting socially relevant categories were presented in a predefined pseudorandom order for a total of 10 minutes. No sound was presented to avoid confounds due to different proficiency in English between participants (22 ASD, 25 NT).

C Stimulus-driven timevarying synchrony of brain activity was estimated with intersubject phase synchronization (ISPS^[4]). Connectivity matrices were created within and between 273 regions from Brainnetome^[5] and Cerebellar connectivity^[6] atlases to measure local ISPS and intersubject functional connectivity (ISFC). Bootstrapping with temporal shifting was used to produce null distribution of synchrony. Differences of within-group synchrony values were calculated and significance was estimated using permutations of group labels.

Orienting toward communication partner is reduced in ASD except in participants scoring high on ADOS

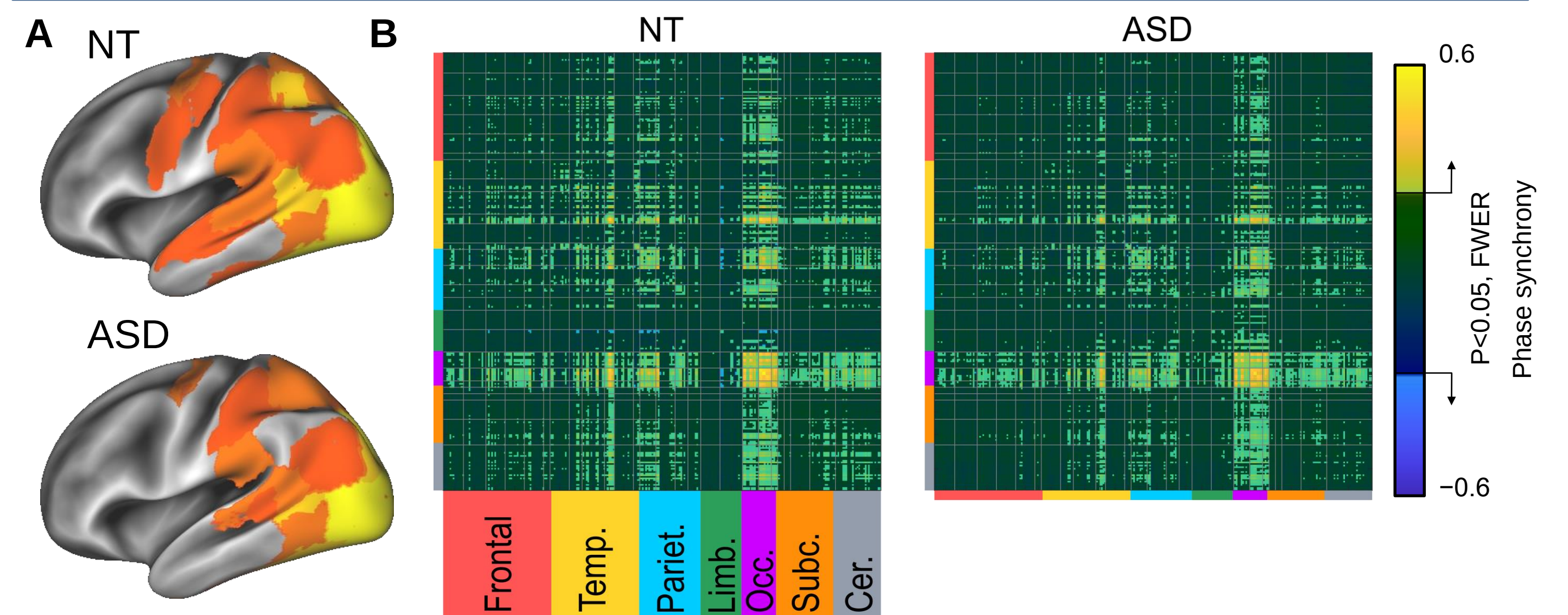


A Mean joint orienting maps for NT and ASD groups. **B** Contrast of orienting behavior between groups. NT spend more time jointly orienting toward interviewer (putative eye contact). **C** Partial correlations controlling for mean group effects show that participants scoring higher on ADOS show abnormally increased orienting toward interviewer, driven mainly by patients. **D** Mean correlations of orienting histograms with all other participant were used to derive a measure of behavioral typicality. All NTs showed highly consistent patterns while typicality for patients was lower, highly variable and correlated with ADOS total scores ($r \sim 0.349$, $p \sim 0.05$).

References

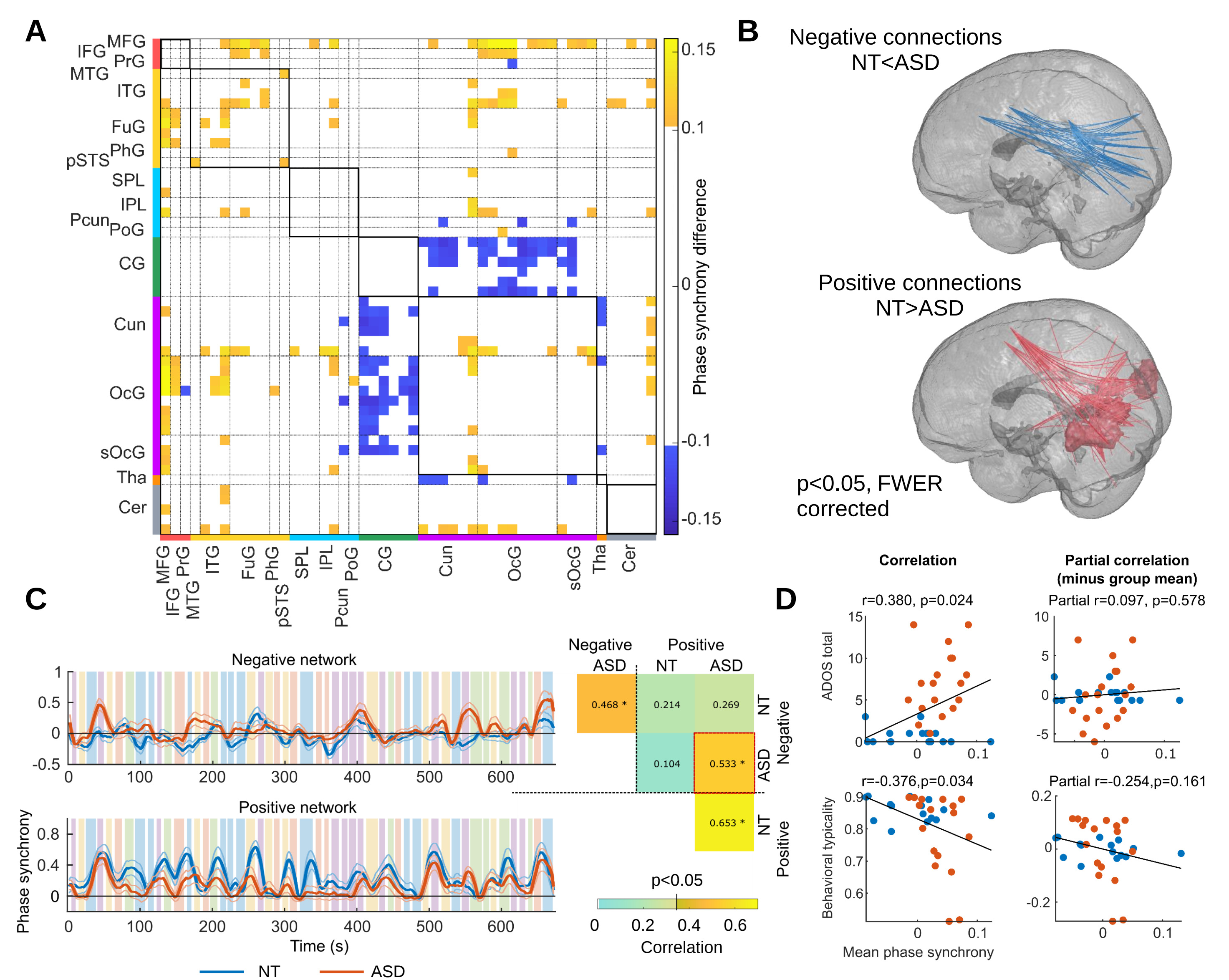
- [1] Lahnakoski et al. (2012) Front Hum Neurosci 6:233 [2] Karjalainen et al. (2017) Cereb Cortex 27: 4257–4266
- [3] Karjalainen et al. (2018) Cereb Cortex 29: 4006–4016 [4] Gleason et al. (2012) Brain connect. 2: 91–101
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Extensive networks of visual and higher order regions synchronize in both groups



A Local ISPS show largely overlapping occipital and parietal regions synchronizing in both groups **B** ISFC between regions shows extensive connectivity of occipital regions as well as parietal, temporal and frontal regions in both groups. Notably, antisynchrony of limbic regions is only observed in the control group. Lobes of the brain are color coded on the sides of the matrices.

Aberrant functional segregation and integration of extrinsic processing in ASD is driven by group and individual differences



A Group differences of ISPS and ISFC values. Only those ROIs are included where group differences exist. Negative connections in NT drive the NT<ASD differences while NT>ASD effects are driven by increased more idiosyncratic activity (lower synchrony) in ASD (“positive connections”). **B** Glass brain visualization of the links shown in panel A. Local ISPS differences are shown as closed surfaces and ISFCs as curved lines between ROIs. **C** Mean synchrony timecourses of the positive and negative connections in ASD (red) and NT (blue) groups, respectively. Correlations between the timecourses are shown in the matrix on the right. Notably, the synchrony of the negative links in ASD is largely similar to the positive links ($r \sim 0.53$, outlined in red) while there is a clear segregation in the NT group as evidenced by low correlation ($r \sim 0.21$) and negative mean synchrony values. **D** Correlations between behavior and typicality of brain activity (mean ISPS compared to all other participants; $N=32$) in the negative connections. Correlations of ADOS with the ISPS (top scatter plots) are driven by a group differences and drop to near zero after removing mean group effects. Behavioral typicality also correlates significantly with ISPS but correlations are not affected as drastically by group mean effects.

Conclusions

- ASD vs. NT orient less toward interaction partner
- ASD patients with high ADOS scores are highly variable and orient more toward the partner than other patients potentially reflecting overcompensation
- Global stimulus-driven functional network patterns are largely consistent
- Aberrant segregation of posterior cingulate/precuneus vs. sensory regions in ASD compared with NT
- ADOS total scores do not predict individual differences of connectivity after controlling for group mean effects
- Behavioral measures show promise for individual prediction beyond group differences
- Future studies will verify reliability and specificity of results against other social interaction disorders in larger samples

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