Restricted and repetitive behaviors (RRBs) are a defining clinical feature of autism spectrum disorders (ASD). RRBs are highly heterogeneous with variable expression of circumscribed interests (CI), insistence of sameness (IS) and repetitive motor actions (RM), which are major impediments to effective functioning in individuals with ASD; yet, the neurobiological basis of CI, IS and RM is unknown. Here we evaluate a unified functional brain circuit model of RRBs and test the hypothesis that CI and IS are associated with aberrant cognitive control circuit dynamics, whereas RM is associated with aberrant motor circuit dynamics. Using task-free fMRI data from 96 children, we first demonstrate that time-varying cross-network interactions in cognitive control circuit are significantly reduced and inflexible in children with ASD, and predict CI and IS symptoms, but not RM symptoms. Furthermore, we show that time-varying cross-network interactions in motor circuit are significantly greater in children with ASD, and predict RM symptoms, but not CI or IS symptoms. We confirmed these results using cross-validation analyses. Moreover, we show that brain-clinical symptom relations are not detected with time-averaged functional connectivity analysis. Our findings provide neurobiological support for the validity of RRB subtypes and identify dissociable brain circuit dynamics as a candidate biomarker for a key clinical feature of ASD.
Restricted and repetitive behaviors (RRBs) have long been recognized as a core symptom of autism spectrum disorders (ASD). RRBs are the earliest detectable behavioral predictors of ASD and have adverse long-term consequences for acquisition of crucial life skills in individuals with the disorder. Critically, recent changes to the Diagnostic and Statistical Manual of Mental Disorders have identified RRBs as central to understanding heterogeneity of clinical presentations in ASD. However, RRBs remain a grossly understudied aspect of ASD research and the underlying brain circuits are unknown. RRBs include behaviors such as preoccupation with objects, ritualized patterns of behavior, highly restricted/fixed interests and stereotyped/repetitive motor (RM) movements. Although RRBs were traditionally defined as a unitary construct, there is growing evidence that RRBs are a heterogeneous construct that can be factored into three distinct phenotypic characteristics: circumscribed interests (CI), insistence on sameness (IS), and RM actions. CI and IS include adherence to routines and restricted patterns of interest and are thought to be cognitive in nature. In contrast, RM includes hand flapping, rocking, and head banging, and are likely to be primarily motoric in origin. Recent evidence suggests that clinical phenotypic features may be more tightly linked to dynamical properties of functional brain circuits as they reflect complex nonlinear neural dynamics and fluctuations in internal mental states. Whether CI, IS, and RM are associated with distinct dynamic brain circuit properties in ASD is currently unknown. Uncovering the brain circuit mechanisms underlying these heterogeneous RRB symptoms/subtypes is important for a more precise understanding of the neurobiolgy of ASD and for further validating the distinctiveness of these individual phenotypic constructs.

Here we address critical gaps in our knowledge regarding heterogeneous expression of RRBs in childhood ASD using dynamic brain circuit analysis. We test the hypothesis that brain circuit dynamics underlying RRB symptoms can be dissociated, and specifically that, aberrant cognitive control circuit dynamics would underlie CI and IS symptoms whereas aberrant motor circuit dynamics would underlie RM symptoms. We characterize the dynamic properties of two distinct brain circuits: (i) a cognitive control circuit consisting of salience (SN)16–18, central executive (CEN)18–20, and default-mode (DMN)21,22 network nodes that play a key role in salience detection, allocation of attentional resources, and flexible behavior and (ii) a motor circuit, consisting of cortical (cMN) and subcortical (sMN) motor network nodes important for implementing motor planning, control, and execution. We predicted that compared to TD children, children with ASD would show less flexible, aberrant time-varying brain circuit dynamics. In addition, we predicted that aberrant dynamics of the cognitive control circuit would be associated with CI and IS symptoms of RRB, but not RM symptoms and that aberrant dynamics of the motor circuit would be associated with RM symptoms of RRB, but not CI and IS symptoms. Finally, we predicted that, compared to static functional circuits, dynamic functional circuits would better distinguish and predict distinct RRB clinical symptoms.

**Temporal dynamics of cognitive control circuit in children with ASD and TD children.** We next examined dynamic, time-varying, cross-network functional interactions in the cognitive control circuit and found four states (temporal clusters) in children with ASD and two in TD children (Fig. 2a, b), reflecting variation in cross-network interactions across time in both groups. Importantly, these results argue against assumptions of stationarity made in most previous functional connectivity studies in ASD.

We then compared the dynamic network interaction index (CNII) of dynamic brain states between the two groups. We computed CNII for each sliding window and averaged CNII for the windows corresponding to the same dynamic brain state. The mean CNII value, averaged across all states, was significantly lower in the ASD group, compared to the TD group (p < 0.0001, t (94) = −4.07, Cohen’s d = 0.83) (Fig. 2c), even after controlling for confounds such as age, sex, head motion, and IQ (Supplementary Table 3). These results demonstrate an intermittent lack of integration of the SN with the CEN and reduced decoupling of the SN from the DMN in children with ASD.

We next compared variability of dynamic time-varying cross-network interactions between the two groups and found that compared to TD children, children with ASD showed greater variability in CNII values across states, suggesting that cross-network interactions in the cognitive control circuit are more variable in ASD than TD group (p < 0.0001, t(94) = 7.27, Cohen’s d = 1.48) (Fig. 2c), even after controlling for confounds (Supplementary Table 4).

The aforementioned results were also observed for a different sliding window length (=40 s) as well as for a different sliding window shape (rectangular), demonstrating that the findings are robust against the length and shape of the sliding window.

**Relation between temporal dynamics of cognitive control circuit and RRB subtypes in children with ASD.** To investigate the extent to which atypical temporal dynamics of the cognitive control circuit is associated with severity of RRB subtypes in ASD, we examined the relationship between features of cognitive control circuit dynamics described above and ADI-R RRB factor scores. Multivariate regression analysis revealed that mean and variability of CNII predicted CI scores (F(2, 45) = 3.9, p < 0.05) and IS scores (F(2, 45) = 3.3, p < 0.05) (see below). There was no significant relationship between mean and variability of CNII and RM (F(2, 45) = 0.48, p = 0.63) (Supplementary Fig. 4), emphasizing the specificity of the finding with CI and IS symptoms. To further examine the predictive ability of CNII, we performed a fivefold cross-validation analysis. Results from this analysis were consistent with the results from the original analysis (r(pred,
The model proposes that aberrant functional organization of key fronto-parietal-opercular cognitive control circuit may contribute to the cognitive components of RRBs i.e., CI and IS symptoms in children with ASD. Specifically, this model posits a key role for the salience network (SN) in aberrant mapping of internal and external salient events leading to altered dynamic temporal interactions with the central executive network (CEN), and the default mode network (DMN), resulting in CI and IS. We next examined dynamic time-varying cross-network interactions within cognitive control circuit and their relationship with CI and IS symptoms. Time-varying cross-network interaction was measured using a dynamic functional connectivity approach. (1) We estimated dynamic functional interactions between SN, CEN, and DMN using a sliding-window approach. (2) To identify distinct group-specific states associated with dynamic functional connectivity, we applied a group-wise k-means clustering on the time-series of correlation matrices in each group separately. (3) Brain state-specific network interaction index (NII) was used to characterize cross-network interaction in each dynamic brain state. NII for each state k by averaging NII across sliding-windows labeled as state k. Cognitive NII (CNI) of a sliding window was computed as the difference in correlation between SN and CEN time series and correlation between SN and DMN. The correlation values were extracted from the covariance matrix associated with that sliding window. Mean and variability of time-varying CNI was calculated as average and standard deviation of CNI values across dynamics brain states respectively. (4) Linear regression analysis was used to examine the relation between dynamic time-varying cross-network interactions measure, including mean and variability of time-varying NII, and ADI-R derived RRB subtype symptom severity scores. The aforementioned results were also observed for a different sliding window length (40 s) as well as for a different sliding window shape (rectangular), demonstrating that the findings are robust against the length and shape of the sliding window.

**Fig. 1 Overall approach to determine the temporal dynamics of cognitive control and motor circuits and its relationship with Restricted and Repetitive Behaviors (RRBs).** a Cognitive control circuit-based model of circumscribed interests (CI) and insistence on sameness (IS) symptoms. The model proposes that aberrant functional organization of fronto-parietal-opercular cognitive control circuit may contribute to the cognitive components of RRBs i.e., CI and IS symptoms in children with ASD. Specifically, this model posits a key role for the salience network (SN) in aberrant mapping of internal and external salient events leading to altered dynamic temporal interactions with the central executive network (CEN), and the default mode network (DMN), resulting in CI and IS. b Overall analysis pipeline for examining dynamic time-varying cross-network interactions within cognitive control circuit and their relationship with CI and IS symptoms. Time-varying cross-network interaction was measured using a dynamic functional connectivity approach. (1) We estimated dynamic functional interactions between SN, CEN, and DMN using a sliding-window approach. (2) To identify distinct group-specific states associated with dynamic functional connectivity, we applied a group-wise k-means clustering on the time-series of correlation matrices in each group separately. (3) Brain state-specific network interaction index (NII) was used to characterize cross-network interaction in each dynamic brain state. NII for each state k by averaging NII across sliding-windows labeled as state k. Cognitive NII (CNI) of a sliding window was computed as the difference in correlation between SN and CEN time series and correlation between SN and DMN. The correlation values were extracted from the covariance matrix associated with that sliding window. Mean and variability of time-varying CNI was calculated as average and standard deviation of CNI values across dynamics brain states respectively. (4) Linear regression analysis was used to examine the relation between dynamic time-varying cross-network interactions measure, including mean and variability of time-varying NII, and ADI-R derived RRB subtype symptom severity scores. The aforementioned results were also observed for a different sliding window length (40 s) as well as for a different sliding window shape (rectangular), demonstrating that the findings are robust against the length and shape of the sliding window.
Relation between temporal dynamics of motor circuit and RRB subtypes in children with ASD. To investigate the extent to which atypical temporal dynamics of the motor circuit is associated with severity of RRB subtypes in ASD, we examined the relationship between features of motor circuit dynamics described above and ADI-R RRB factor scores. Regression analysis revealed that mean of MNII predicted RM scores \((F(1, 46) = 5.2, p < 0.05)\) (Fig. 4c). There was no significant relationship between mean MNII and CI \((F(1, 46) = 0.45, p = 0.5)\) and IS \((F(1, 46) = 3.3, p = 0.07)\) (Supplementary Fig. 4), emphasizing the specificity of this finding. To further examine the predictive ability of MNII, we performed fivefold cross-validation analysis. Results from this analysis were consistent with the results from the original analysis \((r_{\text{pred, actual}})_{\text{RM}} = 0.29, p_{\text{RM}} = 0.005; r_{\text{pred, actual}})_{\text{CI}} = -0.20, p_{\text{CI}} = 0.53; r_{\text{pred, actual}})_{\text{IS}} = 0.13, p_{\text{IS}} = 0.09)\). Similar results were observed with a tenfold cross-validation analysis (see Supplementary Materials for details), highlighting the stability of the findings. This finding was replicated with RM, CS, and IS scores computed using RRB factor weights previously published by Lam and colleagues\(^9\) (see Supplementary Results). Importantly, the brain-behavior relation was not detected with measures of static/time-averaged functional interactions in the motor circuit, demonstrating the specificity of the findings to dynamical properties of the motor circuit (see Supplementary Materials for details).

**Discussion**

The present study addresses a critical gap in our knowledge of brain circuits underlying CI, IS, and RM, three distinct symptom clusters that define RRB—a core clinical phenotype of ASD—in affected children. Using a systems neuroscience-based approach and dynamic functional circuits analysis we provide evidence that childhood ASD is characterized by aberrant dynamics of multiple brain states.
functional brain circuits, and crucially, that cognitive (CI, IS) and motoric (RM) RRB symptoms are associated with unique neurobiological signatures. Our findings demonstrate that dynamic properties of brain circuits can provide fundamental insights into mechanisms underlying heterogeneity of clinical symptoms in ASD.

Our dynamic connectivity analysis revealed that children with ASD have less flexible cognitive control circuit dynamics, characterized by brain states with impaired coupling of the SN with CEN and DMN, consistent with findings from a recent study that reported that adults with ASD show dominant neural states with aberrant functional interactions between SN and CEN and between SN and DMN26. Notably, we found that CI and IS symptoms of RRB were associated with the degree of inflexible interactions between the three key cognitive control networks: SN, CEN, and DMN16,27. Specifically, severity of CI and IS symptoms was associated with aberrant temporal engagement of the SN with the CEN and DMN. Notably, no such relation was found with RM symptoms pointing to the specificity of our findings with respect to cognitive inflexibility. Critically, no static time-averaged functional connectivity measures predicted CI or IS symptoms. These findings demonstrate that aberrant circuits dynamics associated with SN, CEN, and DMN carry clinically relevant neurobiological signatures of cognitive, but not motoric, components of RRB.

Cross-network interactions between the SN, CEN, and DMN play a key role in effectively responding to dynamic demands of changing environment16,27. In particular, interactions of the SN with the CEN and the DMN are thought to facilitate switching between externally-oriented attention and internally-oriented mental processes in response to salient events to guide flexible behavior16,27. Our dynamic network analysis revealed that this
switching is impaired in children with ASD, and that the degree of impairments predicts cognitive inflexibility. These results are consistent with and extend previous studies based on static time-averaged measures demonstrating hyper-connectivity within the SN, CEN, and DMN in children with ASD. Aberrant functioning of the anterior insula node of the SN in ASD may be a key mechanism contributing to inflexible circuits and behaviors given its key role as a social hub for switching between these networks. Together, results suggest that reduced cross-network interactions in the cognitive control circuit contribute to core phenotypic features and inflexible behaviors such as intense focus, unusual attachment to objects of interest, and difficulty with changes in the environment, and provide support for a neurocognitive model of RRB in ASD based on dynamic circuit properties.

Analysis of motor circuit dynamics revealed a different pattern of association with specific RRB phenotypic features. Children with ASD had less flexible motor circuits characterized by stronger intermittent coupling between sMN and cMN. Moreover, we found a strong association between aberrant motor circuit dynamics and RM, but not CI and IS, pointing to the specificity of our findings with respect to motor symptoms. Our results highlight a tight link between sMN-cMN dynamics and RM symptoms observed in children with ASD.

The sMN and cMN nodes including the cerebellum, motor, and premotor regions are critical for motor control and execution, and have been shown to have structural abnormalities in individuals with ASD. Our results suggest reduced differentiation of these motor networks can lead to more rigidity in motor behaviors. We previously suggested that intrinsically hyper-connected circuits may make it more difficult to modulate connectivity in response to task demands, thereby resulting in task-related under-connectivity compared to the baseline state. Consistent with this proposal, a previous study reported reduced static connectivity between the subcortical and cortical motor regions during a finger sequencing task in individuals with autism. Thus, we hypothesize that the propensities of children with ASD to remain in brain states in which sMN and cMN nodes are intrinsically hyper-connected, potentially due to structural deficits in the fronto-thalamo-cerebellum pathway, could lead to inflexible motor control and RM behaviors that are characteristic of the disorder.

To address growing concerns about reproducibility of neuroscientific findings, we leveraged our sample and conducted cross-validation analyses following procedures typically used in machine learning. Cross-validation is a powerful approach for validating research findings, and its use for demonstrating generalization and reproducibility has been advocated in psychiatry, psychology, and many other disciplines. The results of these analyses were consistent with our original results, demonstrating the robustness of our findings. Finally, findings were replicated with RRB measures derived from a previously published factor structure.

In conclusion, the present study is the first to demonstrate that CI, IS, and RM behaviors, the three phenotypic components of RRB, are associated with distinct features of brain circuit dynamics in childhood ASD. In contrast, such brain-clinical symptom associations were not observed with static time-averaged connectivity measures. Future work is needed to determine whether these findings, observed in a predominantly male sample consistent with extant neuroimaging studies of ASD, extend to females with ASD, using 6 min fMRI scans, extend to longer scans, and using ADI-R, extend to other RRB scales such as Repetitive Behavioral Scale-Revised (RRBS-R). Our findings of inflexible functional circuits provide a dynamic brain circuit model of RRB subtypes. Identification of unique neurobiological signatures underlying these symptoms may assist in the development of symptom-based biomarkers and treatments, including TMS that target cognitive control and motor circuits deficits identified here, in affected individuals. Importantly, our findings provide, to the best of our knowledge, novel neurobiological support for the validity of RRB subtypes. More generally, the parsimonious predictive framework and computational methods developed here may prove widely useful for better characterizing clinical heterogeneity in other psychiatric disorders based on systems-neuroscience based models of brain circuit dynamics.

**Methods**

**Participants.** The clinical part of the study wherein we examined the structure of the RRB symptoms included 126 children with ASD (112 males, 14 females; age: 10.0 ± 1.6 years; IQ: 110 ± 16). The imaging part of the study included: 48 children with ASD (41 males, 7 females; age: 10.9 ± 1.9 years; IQ: 115 ± 16) and 48 age- and gender-matched TD children (41 males, 7 females; age: 10.9 ± 1.7 years; IQ: 118 ± 11) (Supplementary Table 1 and Supplementary Fig. 1). Informed written consent was obtained from the legal guardian of each child and the study protocol was approved by the Stanford University Institutional Review Board. The ASD diagnosis procedure and the subject inclusion/exclusion criteria are described in detail in Supplementary Materials.

We also conducted a search (Supplementary Fig. 2) of publicly-available open-source ASD datasets including ABIDE (http://fcon_1000.projects.nitrc.org/indi/abide/) and the NIMH Data Archive (https://nda.nih.gov/) and found that none of these data contain item-level ADI-R scores, crucial phenotypic data relevant to our study, highlighting the uniqueness of our data.

**Clinical measures and analysis.** Similar to previous studies, we used ADI-R to assess RRBs in each child with ASD. To determine the factor structure of the RRB symptom domain as measured by the ADI-R, we performed a PCA with varimax rotation on ADI-R items, using Matlab R2018b. In line with procedures described...
in previous studies, nine ADI-R items which assess RRBs were included in the analysis (Supplementary Table 2). "Current" behavior ratings were used and scores of 6, 7, and 8 were converted to 0. The number of components extracted in PCA was determined using a combination of eigenvalues above 1 and scree plot.

**Imaging data acquisition.** Each participant underwent a 6-min resting-state fMRI scan and a T1-weighted structural imaging scan on a 3 T GE Signa scanner in the same session. Participants were instructed to stay awake, keep their eyes closed, and try not to move for the duration of the 6-min scan. Imaging data acquisition protocol and parameters are described in detail in Supplementary Materials.

**Imaging data analysis.** Overall imaging data analysis pipeline is illustrated in Fig. 1. Imaging data were preprocessed14 (see Supplementary Materials for details) and the preprocessed resting-state fMRI data were entered into a group independent component analysis (ICA) to identify SN, left CEN, right CEN, DMN, cMN, and sMN.

**Dynamic functional brain circuit analysis.**

**Cognitive control circuit.** We applied dynamic functional connectivity analysis on the SN, CEN, and DMN timeseries data in each group (see Supplementary Materials for details and Supplementary Fig. 3). Briefly, we first estimated dynamic functional interactions between SN, CEN, and DMN using an exponentially decaying sliding window. Second, we identified distinct group-specific states associated with dynamic functional connectivity, using group-wise k-means clustering. The optimal number of clusters, i.e., states, was determined using maximal silhouette across multiple iterations.99 Because our goal was to investigate whether dynamic temporal properties differed between the two groups (children with ASD and TD children), we allowed the number of clusters to differ between the groups, instead of keeping them exactly the same.14 Third, we characterized cross-network interaction in each dynamic brain state, using brain state-specific CNII. CNII measures cross-network interactions among the three networks based on the hypothesized role of the SN in switching interactions with the CEN and DMN.16,17 CNII has the advantage of capturing interactions simultaneously among all three networks. Specifically, CNII was computed as the difference in correlation between SN and CEN time series and correlation between SN and DMN. CNII thus captures the extent to which SN temporally engages with CEN and dissociates itself from DMN.6,7,8 We computed CNII for each sliding window and the (i) mean and (ii) variability (measured by standard deviation) of time-varying CNII across all the dynamic brain states for each participant. We then examined the difference between the mean and variability of time-varying CNII between the two groups using two sample t-tests. Non-parametric linear regression was used to test associations between time-varying functional connectivity metrics of the cognitive control circuit and RRB subtypes. To further examine the predictive ability of cognitive control circuit dynamics and assess reproducibility, we leveraged our sample and conducted fivefold and tenfold cross-validation analyses37,38,40 (see Supplementary Materials for details).

**Motor circuit.** We applied dynamic functional connectivity analysis procedures on the cMN and sMN timeseries data in each group (see Supplementary Materials for details and Supplementary Fig. 3). Briefly, we first estimated dynamic functional interactions between cMN and sMN using an exponentially decaying sliding window. Second, we identified distinct group-specific states associated with dynamic functional connectivity, using group-wise k-means clustering. Third, we characterized cross-network interaction in each dynamic brain state, using brain state-specific MNII. MNII measures cross-network interactions among the two networks involved in motor function and was computed as the correlation between cMN and sMN time series. MNII thus captures the extent to which cMN temporally engages with sMN. We computed MNII for each sliding window and the (i) mean and (ii) variability (measured by standard deviations) of time-varying MNII across all the sliding windows for each participant. We then examined the difference between the mean and variability of time-varying MNII between the two groups using two sample t-tests. Non-parametric linear regression was used to test associations between time-varying functional connectivity metrics of the motor circuit and RRB subtypes. To further examine the predictive ability of motor circuit dynamics, we used fivefold and tenfold cross-validation analyses (see Supplementary Materials for details).

**Reporting summary.** Further information on research design is available in the Nature Research Reporting Summary linked to this article.

**Data availability**

All data that support the findings of this study are available from the corresponding authors upon reasonable request.

**Code availability**

Data were analyzed using Matlab 9.5 (R2018b) and SPM8. Data analysis scripts will be made available via GitHub upon publication.

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Author contributions

K.S. and V.M. conceived and designed the study; K.S. analyzed the data; S.R. and P.M. contributed methods; K.S. and V.M. wrote the paper.

Competing interests

The authors declare no competing interests.

Additional information

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