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Altered Cerebro-Cerebellar Dynamic Functional Connectivity in Alcohol Use Disorder: a Resting-State fMRI Study

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Abstract

Alcohol use disorder (AUD) is widely associated with cerebellar dysfunction and altered cerebro-cerebellar functional connectivity (FC) that lead to cognitive impairments. Evidence for this association comes from resting-state functional magnetic resonance imaging (rsfMRI) studies that assess time-averaged measures of FC across the duration of a typical scan. This approach, however, precludes the assessment of potentially FC dynamics happening at faster timescales. In this study, using rsfMRI data, we aim at exploring cerebro-cerebellar FC dynamics in AUD patients ($N = 18$) and age- and sex-matched controls ($N = 18$). In particular, we quantified group-level differences in the temporal variability of FC between the posterior cerebellum and large-scale cognitive systems, and we investigated the role of the cerebellum in large-scale brain dynamics in terms of the temporal flexibility and integration of its regions. We found that, relative to controls, the AUD group exhibited significantly greater FC variability between the cerebellum and both the frontoparietal executive control ($F_{1,31} = 7.01$, $p(\text{FDR}) = 0.028$) and ventral attention ($F_{1,31} = 7.35$, $p(\text{FDR}) = 0.028$) networks. Moreover, the AUD group exhibited significantly less flexibility ($F_{1,31} = 8.61$, $p(\text{FDR}) = 0.028$) and greater integration ($F_{1,31} = 9.11$, $p(\text{FDR}) = 0.028$) in the cerebellum. Finally, in an exploratory analysis, we found distributed changes in the dynamics

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of canonical large-scale networks in AUD. Overall, this study brings evidence of AUD-related alterations in dynamic FC within major cerebro-cerebellar networks. This pattern has implications for explaining the development and maintenance of this disorder and improving our understating of the cerebellum's involvement in addiction.

Keywords

Cerebellum; Alcohol use disorder; Resting-state fMRI; Cerebro-cerebellar networks; Dynamic functional connectivity

Introduction

Alcohol use disorder (AUD) is a chronic and relapsing medical condition characterized by uncontrolled consumption of alcohol that induces a spectrum of negative effects on the brain [1]. Three decades of magnetic resonance imaging (MRI) have extensively highlighted the negative consequences of AUD on selective brain regions and large-scale brain networks, providing a powerful non-invasive, in vivo view of the neurobiological underpinnings of cognitive impairments, impulsive decision making, compulsive alcohol seeking, and the emotional distress associated with alcoholism [2–4]. In this context, evidence suggests that the cerebellum and its functional and structural circuits, notably with prefrontal cortex, are highly vulnerable to alcohol-related damage [5–7]. In short, structural MRI studies have reported significant reduction in grey matter volumes in the cerebellum [6], and have found substantial damage to frontal and cerebellar white matter pathways associated with the severity of alcohol dependence [8–10]. Moreover, task activation and resting-state functional MRI (rsfMRI) studies have consistently reported abnormal activity in the cerebellum of AUD patients, coupled with altered frontocerebellar functional connectivity (FC) and associated with cognitive impairments mainly affecting executive functions [5, 11–15].

The cerebellum has been traditionally associated with motor control, but recent functional neuroimaging studies point to its involvement in cognitive and affective processing [16–19]. In addition, damage to the posterior cerebellum, which can induce disruptions in connectivity between the cerebellum and association and limbic cortices, has been shown to cause the cerebellar cognitive and affective syndrome (CCAS), a constellation of cognitive deficits in executive functioning, language, behavioural inhibition, and emotion regulation [20]. Thus, the cerebellum is believed to monitor and control cognitive processes, thereby maintaining healthy cognitive processing and harmonious behavior [19, 21, 22]. In AUD, selective cognitive, and affective processes are impaired and are deemed inefficient. This inefficiency possibly arises from functional disorganization caused, at least in part, by dysfunction in the connections of the posterior cerebellum to prefrontal association regions and the limbic system, as described by the CCAS paradigm [11, 20, 23, 24]. Furthermore, studies have shown that AUD patients performing well on cognitively demanding tasks tend to recruit unaffected intact loops to compensate for functionally degraded ones normally used by healthy controls for task performance, suggesting compensatory functional reorganization within the cerebellum of those patients [12]. These findings are predicated on observations of reduced FC within certain frontocerebellar executive control loops paralleled

by an increase in FC strength within adjacent unaffected loops [11, 12]. Thus, the disruption of cerebro-cerebellar functional coupling contributes, on one hand, to the characteristic behaviors of AUD, and on the other hand, lead to compensation for the so-called frontally based dysfunctions in alcoholism [25].

So far, most of what we know about the role of the cerebellum and cerebro-cerebellar circuits in AUD comes from studies treating FC as a “static” quantity that does not change across an fMRI scanning session. However, the brain is dynamic, continuously integrating information and reconfiguring to adapt to various changes in the internal and *external milieu* [26]. Therefore, the static FC approach is believed to average out meaningful variations in FC happening at timescales much shorter than a typical fMRI scan [27, 28]. In response to the limitations of traditional approaches, researchers have begun exploring “dynamic” FC, with findings indicating that the brain navigates through a set of transiently recurring FC configurations that encode ongoing fluctuations in cognitive state, even during rest [27, 29–31]. Measures of dynamic FC have been shown to outperform those of static FC in predicting individual differences in learning capabilities [32], executive functioning [33], attention [34], and cognitive flexibility [35], to name a few. In addition, patients with brain disorders including, among others, autism [36], schizophrenia [37, 38], and substance use disorders [39] have been shown to exhibit alterations in dynamic FC, associated with disease symptoms.

A handful of studies have investigated the impact of excessive and prolonged use of alcohol on dynamic FC in the brain, with findings showing alterations in sensorimotor control regions [39], the orbitofrontal cortex and insula [40], and, recently, fronto-striatal circuits [41], associated with the severity of alcohol dependence and cognitive decline in alcoholics. Furthermore, a recent study [42] of cerebro-cerebellar dynamic FC in healthy individuals shows significant associations with sub-facets of trait impulsivity, especially sensation seeking, which is a well-known predisposing factor for addiction [43] and a key component in the disease pattern of both AUD and the CCAS [4, 20, 44, 45]. Together, these findings suggest that dynamic FC may have implications for explaining features of the development and maintenance of AUD that traditional methods are blind to. So far, however, evidence for a role of cerebro-cerebellar FC dynamics in AUD remains limited.

In this study, we explored between-group differences in cerebro-cerebellar dynamic FC between a group of AUD patients and a group of unaffected controls, matched to the AUD group on age and sex. Toward this goal, we adopted the sliding window approach [46] to estimate FC within overlapping segments (≈ 1 min) of the BOLD timeseries extracted from a fine-grained map of cerebral and cerebellar regions [47]. With a focus on temporal variability of FC, we examined the extent of variation in FC between the posterior cerebellum and the executive control, attention, salience, and default mode networks. Then, we applied a graph theory-based dynamic network analysis, known as multilayer community detection [33, 48, 49], to characterize AUD-related changes in the dynamics of the brain’s network structure. In particular, we estimated measures, such as flexibility and integration that characterize the network role of the cerebellum in those dynamics [50, 51]. In an exploratory analysis, we computed those measures at the level of large-scale canonical networks to explore AUD-related changes in their connectivity dynamics. Our

specific hypothesis was that dynamic FC within cerebro-cerebellar networks, especially those connecting the cerebellum to the prefrontal cortex, would differ between AUD patients and healthy controls, such that AUD would confer an overall reduction in frontocerebellar FC.

Methods and Materials

Participants and Neuropsychological Tests

This study was approved by the Institutional Review Boards of Stanford University and SRI International and included 18 AUD patients and 18 controls who had participated in previous studies [52–56]. AUD patients were recruited from local outpatient and treatment centers, or during presentations in clinics by project staff and by distribution of flyers at community events. Healthy, control participants were recruited from the local community by flyers. All participants were free of any serious medical, psychiatric, or neurological diseases (e.g., neurodegenerative diseases) at the time of scanning, and provided written informed consent to participate in this study, in accordance with the Declaration of Helsinki, by the signing of consent documents in the presence of staff. All AUD patients were screened using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders to assess the DSM-5 criteria for AUD [57], and were given the Clinical Institute Withdrawal Assessment for Alcohol (CIWA) to assess the severity of alcohol withdrawal. Demographic data of study groups are summarized in Table 1.

Participants completed a comprehensive neuropsychological battery to assess attention, memory and learning, visuospatial abilities, and executive functions. Raw test scores were statistically corrected for age on the control group [mean and standard deviation for control group = 0 ± 1], allowing averaging across tests. Composite scores were then calculated as the mean of all *Z*-scores of tests comprising each of the functional domains. Neuropsychological data were available for all 18 subjects with AUD and 12 of the 18 controls. The comprehensive list of the included tests is as follows:

Attention:

Wechsler Memory Scale-Revised (WMS-R) block forward total

WMS-R block forward span

Memory and Learning:

Wechsler Adult Intelligence Scale (WAIS) digit symbol incidental recall of symbols

WAIS digit symbol incidental recall of numbers

California Verbal Learning Test (CVLT) short delay free recall

CVLT long delay free recall

Montreal Cognitive Assessment (MOCA) delayed recall

WMS-R logical memory story A raw score

WMS-R logical memory story B raw score

Visuospatial Abilities:

- Rey-Osterrieth copy raw score
- WMS-R visual reproduction item 1 raw score
- WMS-R visual reproduction item 2 raw score

Executive Functions:

- Controlled Oral Word Association Test (F + A + S total)
- Semantic fluency (inanimate objects, animals)
- WAIS digit symbol total time to complete set
- WAIS digit symbol standard score at 90 seconds
- MoCA abstraction score

MRI Acquisition

For each participant, a single resting-state fMRI scan and a T1-weighted MRI scan were performed. The resting-state scans were collected with a $1.71 \times 1.71 \times 3$ -mm spatial resolution and 200 time-points (i.e., repetition times; TRs) for each participant. Three protocols associated with slightly different repetition times (TRs) ranging from 2.65 to 2.86 s were used during the study. In particular, 28 participants (16 controls, 12 AUD) were scanned with a TR = 2.65 s, 4 participants (2 controls, 2 AUD) were scanned with a TR = 2.75 s, and 4 participants (4 AUD) were scanned with a TR = 2.86 s. Statistical analysis revealed no effect of TR on group differences (F -tests < 0.1 , p values > 0.05). Therefore, scans from all protocols were included, and TR was not considered a confounding factor in group comparisons.

MRI Data Preprocessing

Functional and structural MRI data were preprocessed using *fmrprep* 20.0.1 [58]. For the structural T1-weighted scans, we performed skull-stripping, segmentation, and normalization to the Montreal Neurological Institute (MNI152) standard space, whereas for the resting-state fMRI scans, we performed slice timing correction, distortion correction, motion correction, co-registration to each subject's T1-weighted scan, normalization to *MNI152* space, resampling to $2 \times 2 \times 2$ mm grid, spatial smoothing (FWHM = 4 mm), and bandpass filtering [0.02–0.1 Hz]. Finally, we regressed out the confounding effects of head motion using *Friston 24-parameter model*, white matter and cerebrospinal fluid signal using the *aCompCor* method [59], and linear and quadratic trends.

Further details for “MRI Data Preprocessing” to “Dynamic Network Analysis: Flexibility and Integration of the Cerebellum” sections are found in Supplementary Material.

Definition of Functional Brain Regions and Networks

We used 300 spherical regions positioned around suggested coordinates in MNI space (see Fig. 1a) to define functional brain regions. This functional map offers a comprehensive view for the study of brain functional modules and their interactions with improved

representations of the cerebellum and the subcortex [47]. In this map, the whole brain is divided into 13 functional systems. Here, however, we focused on the dynamics of FC within the cerebellum and between regions of the cognitive posterior cerebellum and seven large-scale cerebral cognitive systems, namely, the frontoparietal network (FPN), default mode network (DMN), reward network (RN), dorsal and ventral attention networks (DAN and VAN), salience network (SN), and the cingulo-opercular network (CON).

Dynamic Functional Connectivity: Sliding Window Approach

For each participant, whole-brain dynamic FC was modelled using the sliding window approach [46]. In this setup, the BOLD time series from 300 brain regions were divided into overlapping segments (i.e., windows), each spanning 20 timepoints (i.e., TRs). Then within each window, pairwise connectivity was estimated using Pearson's correlation between the time series followed by Fisher r -to- z transform of the coefficients to stabilize their variance. We also performed a supplementary validation analysis using windows of different lengths (15 TR and 25 TR) to assess the robustness of our findings to different parameters.

Temporal Variability of Cerebro-Cerebellar FC

The connectivity patterns between brain regions/networks fluctuate dynamically over short periods of time. Temporal variability of FC is a straightforward measure that can be used to quantify these fluctuations [61]. Here, we estimated the temporal variability of the FC between cerebral regions, belonging to seven large-scale cognitive networks of interest, and the cognitive cerebellum.

For a given cerebral region k , a FC profile at time window w_s is defined as a vector with M values that quantify the connectivity map between region k and all regions of the cognitive cerebellum. Then, temporal variability was computed as an average measure of "dissimilarity" among the FC profiles between region k and the cerebellum extracted from all time windows. Finally, the temporal variability between each large-scale cognitive network and the cerebellum is calculated by averaging the temporal variability scores over all regions belonging to the same network (see Fig. 1c).

Dynamic Network Analysis: Multilayer Community Detection

For each participant, the sliding window approach yielded a time series of three-dimensional 300×300 FC matrices that can be thought of as a large multilayer connectivity matrix. In each layer, there exists a different network organization, reflecting the transient emergence and dissolution of functional communities as patterns of FC change from one window to another. A functional community, in this case, is defined as an ensemble of brain regions that have a strong FC among them and a weak FC with other regions during a short time period ($\approx 50 - 60$ s).

By using a dynamic graph theory method known as multilayer community detection, we delineated the time-varying functional communities across time windows for each participant. To achieve this, the algorithm maximizes a Louvain-like modularity function Q , resulting in the optimal community assignment for each region in each window (see Fig. 1d; [49, 51, 62–64]).

Dynamic Network Analysis: Flexibility and Integration of the Cerebellum

Multilayer community detection also permitted the quantification of the dynamic role of each of the 300 brain regions, as communities emerge, dissolve, and reemerge, using two measures:

- The first measure is *flexibility*, defined as the proportion of time a brain region switches its community affiliation across time windows [32, 33]. For each participant, we computed the flexibility of the cerebellum by averaging flexibility scores over all cerebellar regions.
- The second measure is *integration*, defined as the average probability for a brain region to be assigned to the same community with regions outside its “native” functional system [51, 65]. We computed the integration of the cerebellum for each participant by averaging integration scores over all cerebellar regions.

Finally, in an exploratory analysis, we estimated those measures for each of the seven large-scale cognitive networks by averaging the scores over their constituent regions.

Statistical Analysis

Two-sample *t* tests assessed between-group differences on continuous variables and chi-squared tests for categorical variables. Univariate analyses of covariance (ANCOVAs) tested between-group differences on temporal variability, flexibility, and integration, while controlling for the confounding effects of age, sex, and overall head motion in the scanner. Finally, the false discovery rate (FDR) procedure controlled for the rate of type-I errors at $\alpha = 0.05$ [66]. We did not, however, correct for multiple comparisons in the exploratory analysis. Because the different hypotheses tested were not pre-registered on any online platform, study findings should be considered exploratory.

Results

Group Comparisons: Demographics and Neuropsychological Tests

Groups significantly differed in terms of years of education, socioeconomic status, IQ, Beck depression index, lifetime consumption of alcohol, smoking, and in-scanner head motion. Moreover, the AUD group performed worse than controls on all 4 neuropsychological composite scores: attention ($t = -3.2$, $p = 0.003$), learning and memory ($t = -4.9$, $p < 0.0001$), visuospatial abilities ($t = -3.9$, $p = 0.0007$), and executive functions ($t = -6.9$, $p < 0.0001$). The directionality of these group differences is expected and consistent with previous findings on the typical epidemiology of the AUD group. Demographic data of study groups are summarized in Table 1.

Group Comparisons: Temporal Variability of Cerebro- Cerebellar FC

Results of group comparisons showed that, relative to the controls, the AUD group exhibited significantly greater temporal variability of FC between the cerebellum and two large-scale cognitive networks: FPN ($F_{1,31} = 7.01$, $p(FDR) = 0.028$) and VAN ($F_{1,31} = 7.35$, $p(FDR) = 0.028$). Group differences were not forthcoming in other networks: DMN ($F_{1,31} = 0.144$, $p(FDR) = 0.71$), RN ($F_{1,31} = 0.7$, $p(FDR) = 0.45$), DAN ($F_{1,31} = 0.72$, $p(FDR) = 0.45$), SN

($F_{1,31} = 1.28$, $p(FDR) = 0.45$), and CON ($F_{1,31} = 0.93$, $p(FDR) = 0.45$). Statistical details of group comparisons in temporal variability of cerebro-cerebellar FC are summarized in Table 2 and illustrated in Fig. 2.

Group Comparisons: Cerebellar Flexibility and Integration

On average, the AUD group exhibited significantly less cerebellar flexibility than controls across the fMRI scanning interval ($F_{1,31} = 8.61$, $p(FDR) = 0.028$), indicating that over time, cerebellar nodes switched their community affiliation less frequently in the AUD group than the controls. By contrast, the AUD group demonstrated significantly greater cerebellar integration than controls across the scanning interval ($F_{1,31} = 9.11$, $p(FDR) = 0.028$), indicating that over time, cerebellar nodes that belong to different functional systems tend to communicate with nodes outside their native functional systems more often in the AUD group than in controls. Statistical details of group comparisons in cerebellar flexibility and integration are summarized in Table 3 and illustrated in Fig. 3.

Group Comparisons: Network Flexibility and Integration

Results of group comparisons in the exploratory analysis revealed statistically significant group differences in network flexibility and integration (see Figs. 4 and 5). Specifically, relative to controls, the AUD group exhibited significantly less flexibility in the SN ($F_{1,31} = 21.6$, $p < 0.0001$ uncorrected) and CON ($F_{1,31} = 6.01$, $p = 0.02$ uncorrected). Furthermore, relative to controls, the AUD group exhibited significantly greater integration in the FPN ($F_{1,31} = 5.4$, $p = 0.026$ uncorrected) (Table 4).

Discussion

Previous studies that reported altered cerebro-cerebellar FC in AUD based their findings on measures of static FC that is blind to fast variations in the brain's network structure. Herein, we explored cerebro-cerebellar dynamic FC in AUD using sliding window approach and multilayer community detection. Relative to controls, the AUD group exhibited significantly greater temporal variability of FC between the cerebellum and two cognitive networks: FPN and VAN. Moreover, the AUD group showed significantly less flexibility and greater integration in the cerebellum compared with controls. Finally, exploratory analysis revealed that the AUD group exhibited less flexibility in the SN and CON and greater integration in the FPN. Overall, these results provide evidence of AUD-related alterations in dynamic FC, complementing existing literature on the adverse effects of prolonged, excessive use of alcohol on the brain in general and cerebro-cerebellar networks in particular.

Hypervariability of Cerebro-Cerebellar FC in AUD

Temporal variability of FC is thought to reflect a general readiness of the brain to reorganize in response to changing attentional demands [33, 35, 61, 67, 68]. However, previous studies have shown that hypervariability of FC during rest is a hallmark of brain disorders including schizophrenia, bipolar disorder, autism spectrum disorder, Alzheimer's disease, and Parkinson's disease, potentially reflecting a frequent emergence of a state of dysconnectivity and disrupted exchange of information among brain regions [36, 69–73].

Likewise, our results revealed that, relative to controls, the AUD group exhibited hypervariability of FC between the cerebellum and both the FPN and VAN, suggesting a disorganized FC dynamic and reduced overall connectivity strength within cerebro-cerebellar executive control and attention networks. These networks are involved in top-down cognitive control, working memory, and attention shifting [74–76], which have been shown to be impaired in AUD [77–80]. Although these networks are anchored in the frontal lobe, the coordinated interaction among distributed brain regions, including the cerebellum, is believed to be a critical component for maintaining efficient cognitive functioning [81]. Thus, we hypothesize that the observed hypervariability of cerebro-cerebellar FC within these networks would be associated with deficits in executive function and attention, often attributed to the neurotoxic effects of excessive use of alcohol [1].

Abnormal Cerebellar Flexibility and Integration in AUD

The AUD group showed significantly less flexibility in the cerebellum than controls. Flexibility has been previously associated with diverse cognitive processes including working memory [33], learning [32], attention [82], cognitive flexibility, planning, and processing speed [48, 83], supporting its relevance to cognition and behavior. Moreover, studies of brain disorders have reported abnormally high levels of whole-brain flexibility in patients with schizophrenia and autism, which is thought to reflect temporally less stable, disintegrated, and disordered network dynamics associated with the unique pathophysiology of these disorders [36, 37, 48].

Given that the cerebellum is implicated in AUD, the relative cerebellar inflexibility, during rest, in the AUD group is unlikely to indicate more organized cerebro-cerebellar network dynamics, but rather increased functional rigidity of cerebellar regions across time-varying functional communities. This is likely to reflect a compromised capacity of the cerebellum in AUD to flexibly adapt to environmental changes that require fast reconfiguration of FC patterns and re-organization of brain networks. Nonetheless, this interpretation remains speculative and should be further explored in future studies using externally cued cognitive tasks interspersed by epochs of resting-state, which enable a direct assessment of cerebellar flexibility as environmental conditions change.

We also found that the AUD group exhibited significantly greater integration in the cerebellum than controls. This might reflect compensatory functional remapping in the cerebellum [12], whereby cerebellar regions tend to connect for longer periods with other regions outside their “native” functional systems to promote normal performance on tasks. Recent findings, however, suggest that abnormal cerebellar activity in AUD patients, who are early in abstinence, is unlikely to reflect compensatory re-organization but rather pathological or maladaptive plasticity, especially in the frontal lobe and the cerebellum [84]. In this sense, results from our exploratory analysis also revealed significantly greater integration in the FPN in the AUD group compared to controls. As such, we could also interpret greater integration in the cerebellum and the FPN as a signature of pathological, rather than compensatory, functional re-organization. However, this remains an open question for future studies that explore task-evoked dynamics within the frontocerebellar circuitry.

Exploratory Analysis: Abnormal Large-Scale Network Flexibility in AUD

Results of the exploratory analysis revealed that the AUD group exhibited relatively less flexibility than controls in the salience network (SN) and the cingulo-opercular network (CON). These networks subtend portions of the anterior cingulate cortex, anterior insula/operculum, supplementary motor area, thalamus, and basal ganglia (see Fig. 4c, d), which are highly vulnerable to alcohol-related damage and are purported to take part in the formation of the addiction cycle [81]. Of particular importance, the SN is known to be a highly flexible and versatile network that facilitates the antagonistic activity of the DMN and the executive control and attention networks, promoting cognitive flexibility [85–87]. Altered dynamics between those networks is associated with delayed shifting from internally to externally focused attention, leading to inefficient cognitive processing and delayed responses to changing environmental changes [88]. Considering this, we hypothesize that altered SN dynamics in AUD contributes to commonly reported deficits in cognitive control, memory, and reward/motivation processes [85, 89].

Taken together, the findings from this study corroborate those from the literature suggesting selective and far-reaching alterations in major brain systems encompassing the cerebellum, frontal lobe, and the basal forebrain in AUD [1, 6, 90]. In particular, this study comes in line with previous findings showing that the disruption of cognitive cerebro-cerebellar networks, especially the executive frontocerebellar circuitry, is associated with characteristic behaviors of alcoholism that, on the one hand, enable alcohol use disorders, and on the other hand, may lead to compensation for so-called frontally based dysfunctions in alcoholism. Specifically considered, is the possibility that in AUD cerebellar degeneration and the compromise of the functional dynamics in executive loops may contribute to dysfunction in standard neuropsychological testing as well as inefficiency of information processing, interpersonal problem solving, impulse control [44, 91], conflict processing [92], and behavioral disinhibition [93] that enable maintenance of the addictive behavior. In this context, present findings report AUD-related deficits in all four neuropsychological domains assessed, which is in accordance with the literature that AUD individuals have detectable cognitive impairments, often involving executive dysfunction, attention deficits, and reduced cognitive control (see reviews [1, 79]).

Limitations

Important limitations that could affect the reliability of current findings are the small sample sizes and number of timepoints, which may be sub-optimal for dynamic FC analysis. Future studies should validate current findings using larger sample sizes, longer scanning periods, and multiple fMRI sessions. Another limitation is that the groups were not matched with respect to years of education, socioeconomic status, IQ, depressive symptoms, and smoking status. However, the directionality of these group differences is expected based on the typical epidemiology of the AUD group. A third limitation is the lack of detail at the level of the cerebellum and large-scale brain networks. Therefore, future studies, guided by specific hypotheses, should explore features of dynamic FC at the level of cerebellar sub-modules for a more comprehensive view of AUD-related alterations in the cerebellum.

Conclusion

To the best of our knowledge, this is the first study to bring evidence of altered cerebro-cerebellar dynamic FC in AUD. Our analysis shows that AUD patients exhibit hypervariability in cerebro-cerebellar networks subserving executive control and attention as well as abnormalities in the network role of the cerebellum at fast timescales. Adding to previous findings, our results suggest that AUD confers alterations to cognitive cerebro-cerebellar networks at different temporal and topological scales. Longitudinal studies will be essential for determining whether the features of cerebro-cerebellar dynamic FC are trait characteristics for the development and maintenance of AUD or are state characteristics that may change with sustained sobriety.

Finally, the present findings may provide an impetus for further studies on the dynamic interactions among functional brain networks that subserve executive functioning, cognitive flexibility, and attention and their role in the etiology and pathophysiology of substance use disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Acronyms

AUD	alcohol use disorder
CON	cingulo-opercular network
DAN	dorsal attention network
DMN	default mode network
FC	functional connectivity
FPN	fronto-parietal network
RN	reward network
ROI	region of interest
RsfMRI	resting-state functional magnetic resonance imaging
SN	salience network
VAN	ventral attention network

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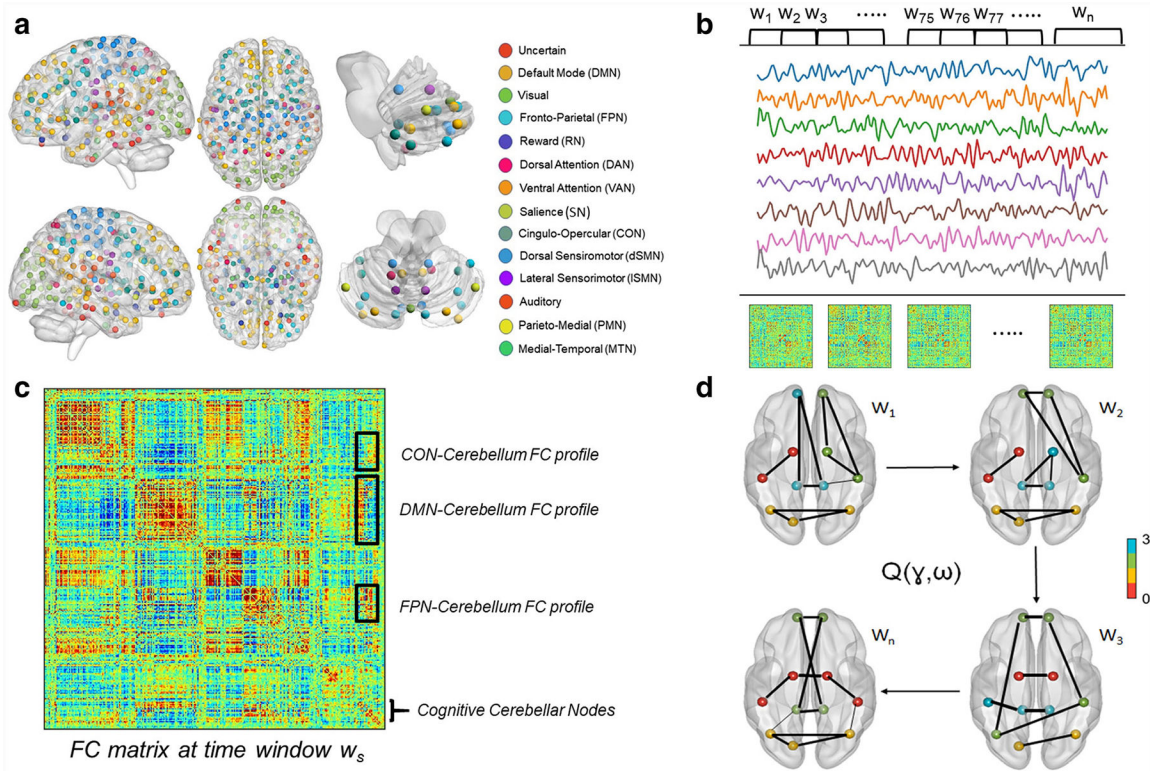
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**Fig. 1.**

Schematic overview of the main methods used in this study. **a** Whole-brain parcellation using functionally defined regions of interest with an improved representation of the cerebellum and the subcortex. **b** BOLD signals from all ROIs were segmented into overlapping windows using the tapered sliding window analysis, and a whole-brain FC matrix was constructed by computing pairwise Pearson's correlation in each window. **c** An example FC matrix in an arbitrary time window w_s . The FC profile between distinct cerebral cognitive networks and the cerebellum is a sub-matrix (shown as boxes marked by black lines) containing the FC weights between its constituent nodes and every node in the cognitive cerebellum. Then, temporal variability of FC was calculated as the extent of variation of cerebro-cerebellar FC profiles across time windows. **d** Maximizing the multilayer modularity quality function $Q(\gamma, \omega)$ helps detecting the optimal community assignment for each node in each window. Using the optimal community structure, we calculated flexibility as the proportion of time a node changes its community assignment in time. Also, we calculated integration as the average probability for a node to be assigned to the same community with nodes outside its native system. Brain networks were visualized with the BrainNet Viewer toolbox <http://www.nitrc.org/projects/bnv/> [60]

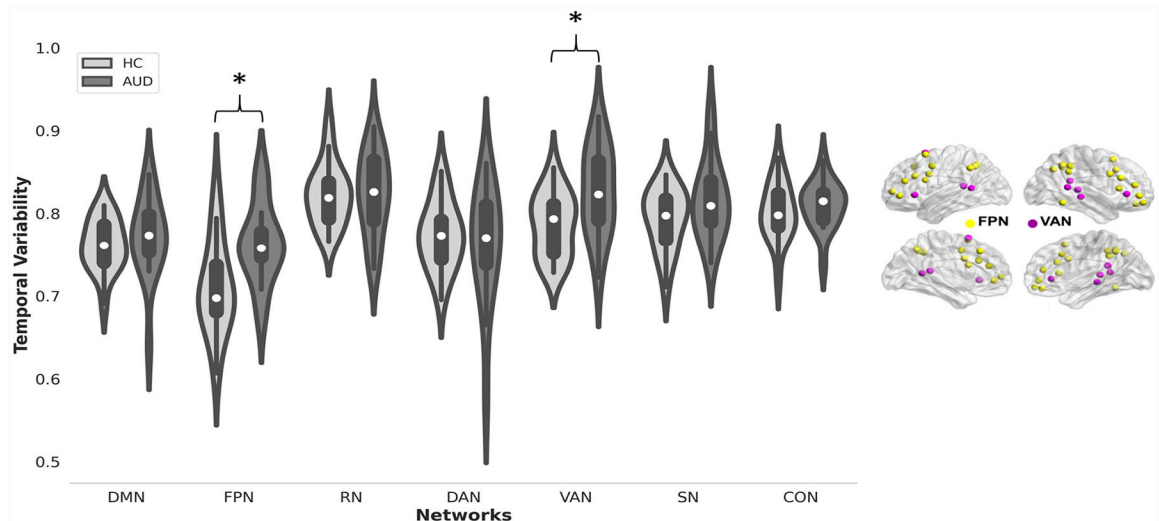


Fig. 2. (Left) Violin plots of temporal variability of FC between the cerebellum and seven large-scale cognitive networks for the AUD group and controls. Asterisk indicates $p < 0.05$ (FDR corrected) for group differences. (Right) Brain plot of the frontoparietal and ventral attention networks

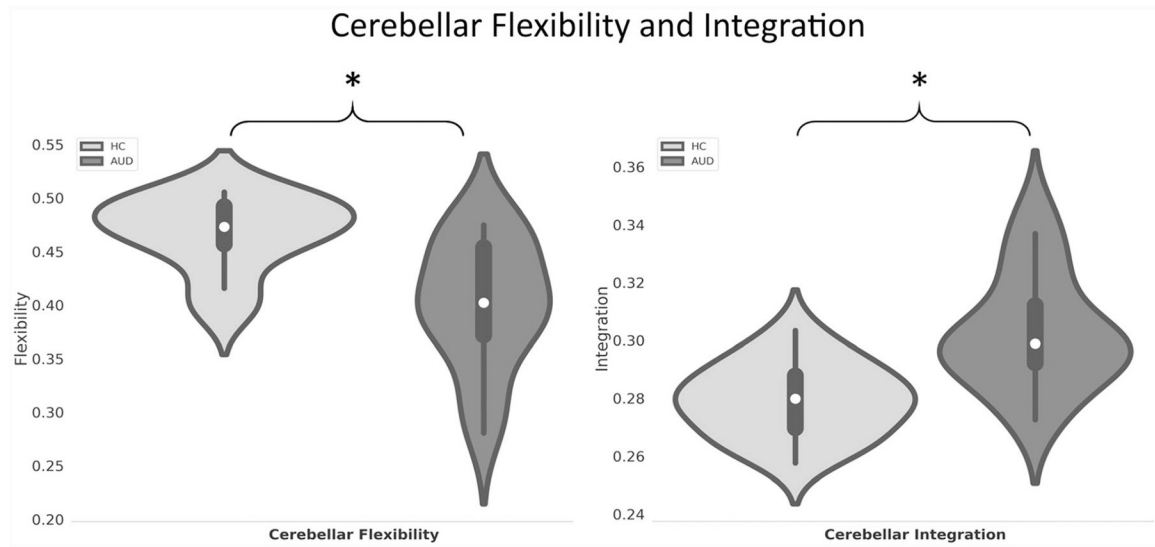


Fig. 3. Violin plots of cerebellar flexibility and integration (right) for the AUD group and controls. Asterisk indicates $p < 0.05$ (FDR corrected) for group differences

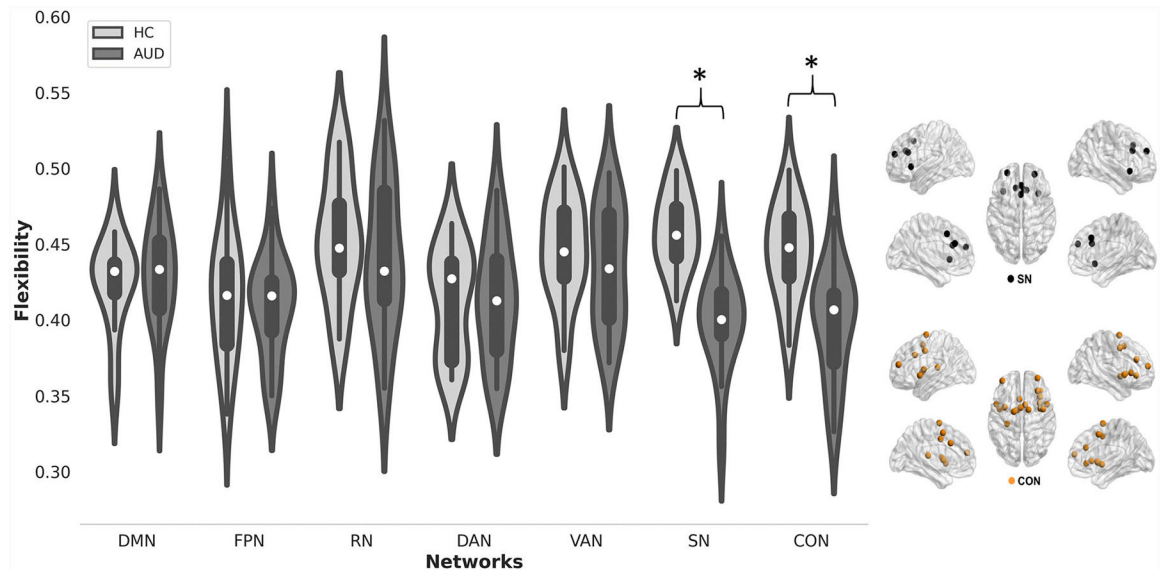


Fig. 4. (Left) Violin plots of network flexibility for the AUD group and controls. Asterisk indicates $p < 0.05$ (uncorrected) for group differences. (Right) Brain plots of the salience and cingulo-opercular networks

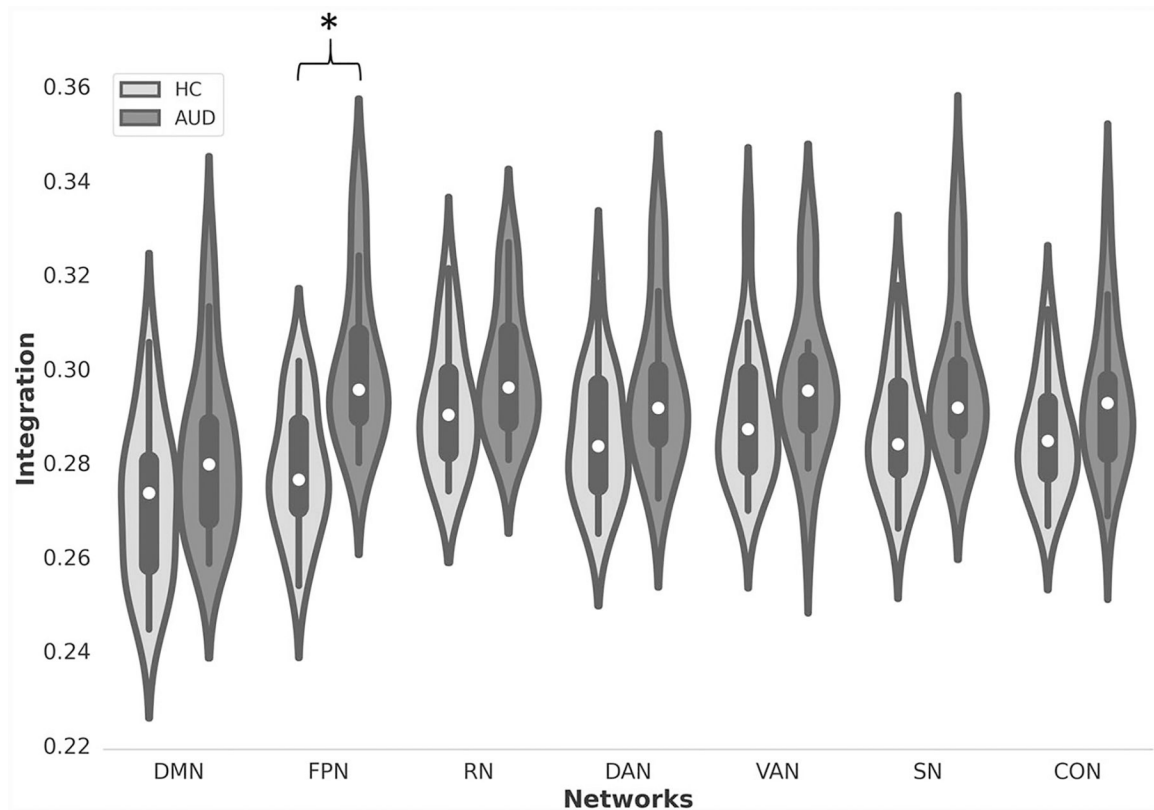


Fig. 5. Violin plots of network integration for the AUD group and controls. Asterisk indicates $p < 0.05$ (uncorrected) for group differences

Table 1

Demographic data of study groups: mean ± SD/frequency count

Demographic variable	Controls (n = 18)	AUD (n = 18)	p value
Sex (male/female)	10/8	13/5	0.49
Age (years)	48.8 ± 8.81	53.2 ± 8.76	0.13
Handedness (right/left)	18/0	15/3	0.23
Ethnicity (Caucasian/African/American/Asian)	10/2/6	13/4/1	0.1
Education (years)	17.2 ± 2.57	12.7 ± 1.82	< .0001
Socioeconomic status	19.72 ± 11.46	41.28 ± 12.8	< .0001
[‡] WTAR predicted IQ	104.23 ± 6.2	96.7 ± 8.34	0.01
[‡] Beck Depression Index	4 ± 4.08	13.6 ± 11.12	< .0001
AUD onset age	—	21.83 ± 6.91	—
Lifetime alcohol consumption (kg)	61.4 ± 93.2	1567.67 ± 1165.86	< .0001
Days since last drink	—	105.26 ± 102.63	—
CIWA total score	—	27.68 ± 15.5	—
DSM-5 AUD total score	—	9.37 ± 2.26	—
Smoker (never/past/current)	18/0/0	4/5/9	< .0001
In-scanner head motion (mm)	0.1 ± 0.04	0.18 ± 0.09	.0003

[‡]Some subjects in both groups had missing data on WTAR-IQ and Beck Depression Index

t tests were used on continuous variables (e.g., age); χ^2 tests were used on nominal variables to assess group differences

Bold indicates significant differences between groups

Results of group comparisons in temporal variability of FC between seven large-scale networks and the cerebellum

Table 2

Network	Controls mean (SD)	AUD mean (SD)	$F_{1,31}$	p value (FDR)	η_p^2
DMN	0.76(0.03)	0.77(0.046)	0.14	0.71	0.005
FPN	0.71(0.055)	0.76(0.046)	7.01	0.028	0.18
RN	0.82(0.036)	0.82(0.048)	0.7	0.45	0.02
DAN	0.77(0.04)	0.76(0.07)	0.72	0.45	0.02
VAN	0.79(0.04)	0.82(0.052)	7.34	0.028	0.19
SN	0.8(0.035)	0.82(0.045)	1.28	0.45	0.04
CON	0.8(0.033)	0.81(0.027)	0.93	0.45	0.03

AUD alcohol use disorder, SD standard deviation, FDR false discovery rate, FF-statistic, η_p^2 partial eta-squared effect size, DMN default mode network, FPN fronto-parietal network, RN reward network, DAN dorsal attention network, VAN ventral attention network, SN salience network, CON cingulo-opercular network

Bold indicates significant between-group difference

Table 3

Results of group comparisons in flexibility and integration in the cerebellum

Score	Controls mean (SD)	AUD mean (SD)	$F_{1,31}$	p value (FDR)	η_p^2
Flexibility	0.45(0.033)	0.4(0.06)	8.61	0.028	0.22
Integration	0.28(0.012)	0.3(0.019)	9.11	0.028	0.23

Table 4

Results of group comparisons in network flexibility and integration

Network	Score	Controls mean (SD)	AUD mean (SD)	$F_{1,31}$	p value	η_p^2
SN	Flexibility	0.46(0.025)	0.4(0.03)	21.6	< 0.001	0.42
CON	Flexibility	0.45(0.03)	0.42(0.035)	6.01	0.02	0.15
FPN	Integration	0.28(0.013)	0.3(0.017)	5.4	0.026	0.12