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Craving dynamics and related cerebral substrates predict timing of use in alcohol, tobacco, and cannabis use disorders

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Abstract

Background: Patients treated for Substance Use Disorders exhibit highly fluctuating patterns of craving that could reveal novel prognostic markers of use. Accordingly, we 1) measured fluctuations within intensively repeated measures of craving and 2) linked fluctuations of craving to connectivity indices within resting-state (rs) brain regions to assess their relation to use among patients undergoing treatment for Alcohol, Tobacco and Cannabis Use Disorders

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[‡]Joel Swendsen passed away suddenly on July 14th, 2022. This paper is dedicated to his memory.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.addicn.2023.100138.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Method: Participants —64 individuals with SUD for tobacco, alcohol, or cannabis and 35 healthy controls—completed a week of Ecological Momentary Assessment (EMA) during which they reported craving intensity and substance use five times daily. Before EMA, a subsample of 50 patients, and 34 healthy controls also completed resting-state (rs)-MRI acquisitions. Craving temporal dynamics within each day were characterized using Standard Deviation (SD), Auto-Correlation Factor (ACF), and Mean Successive Square Difference (MSSD). Absolute Difference (AD) in craving between assessments was a prospective prediction measure.

Results: Within-day, higher MSSD predicted greater substance use while controlling for mean craving. Prospectively higher AD predicted later increased substance use independently of previous use or craving level. Moreover, MSSD was linked to strength in five functional neural connections, most involving frontotemporal systems. Cerebello-thalamic and thalamo-frontal connectivity were also linked to substance use and distinguished the SUD from the controls.

Conclusion: To the best of our knowledge, this is the first study to indicate that instability in craving may be a trigger for use in several SUD types, beyond the known effect of craving intensity.

Keywords

Craving; Substance use; EMA; Resting state; Dynamic; Markers

Introduction

Substance Use Disorders (SUD) are consistently ranked among the greatest contributors to Global Burden of Disease estimates [1–3] and represent the most frequent forms of mental illness in the general population [4,5]. Over recent decades, treatments for these conditions have increasingly focused on craving management due to its nearly ubiquitous presence across the wide diversity of SUD as well as for its major role in relapse [6,7]. A recent meta-analysis suggested that despite strong evidence for the causal involvement of craving in risk of use, the variability that craving displayed, both between [6] and within individuals [8], could explain the heterogeneity of response to SUD treatments for all drug types [6]. We hypothesized that the characterization of craving's fluctuations over time along with its underlying cerebral bases could reveal new potential markers of use vulnerability among patients undergoing treatments for Alcohol, Tobacco, and Cannabis Use Disorders.

Craving assessment has most often adopted a dimensional approach through tools that provide continuous measures of craving intensity [6]. Apart from SUD, recent literature on other psychiatric disorders has demonstrated the importance of considering the dynamic variability of symptoms and risk factors rather than focusing solely on averages or momentary intensity level [9–14]. The traditional approach includes the characterization of a single feature of the dynamic, such as variability indexed by Standard Deviation or temporal instability, or inertia indexed by an autocorrelation factor (ACF) [15]. Other measures take into account variability and temporal dependency simultaneously to characterize instability. The Mean Square Successive Differences (MSSD) index describes time-to-time fluctuations, that is, the trends in the measurements, and is considered a better proxy of the regulation of a

process than its global variability or temporal stability [15] and could be suited to define the complexity of craving's fluctuations.

Although methodologically challenging, the characterization of such dynamics in daily life is possible through Ecological Momentary Assessment (EMA) by implementing repeated assessments of craving and substance use on a smartphone [16]. In SUD populations, a systematic review including 53 EMA studies examining the link between craving and subsequent substance use, 92 % showed that temporary craving increased the risk of substance use both concurrently and at the next sampling time [6,17]. Some studies using indexes of variability that did not take into account temporal stability such as SD or Mean Absolute Deviation were successful in demonstrating an impact of craving variability on substance use [18,19]. More recently, two studies investigated the dynamic of craving using MSSD, taking into account both variability and temporal stability: one comparing persons with or without psychotic disorders [20], and the other showing an impact on use beyond the mean level of craving in opioid use disorder [21]. While promising, these studies did not examine two high priority factors needed to advance a mechanistic understanding of SUD: identification of shared prognostic features across different types of SUD, and cerebral markers of prognostic factors [22].

Both needs can be simultaneously fulfilled by coupling EMA characterization of craving dynamics in Alcohol, Tobacco and Cannabis Disorders with neuroimaging. The complementarity of both methods has been highly promoted [23], and multiples studies emphasized its feasibility and pertinence (for a review of MRI and EMA papers until 2020 please see [23]) especially for resting state (rs) fMRI that allows accounting for the wide range of brain regions implicated in this pathology [24]. While rs-fMRI analysis has previously assessed brain networks contributing to craving [24,25], coupling neuroimaging with EMA to investigate brain regional connectivity linked to craving dynamics has not yet been studied.

Previous investigations restricted to the mean index of craving intensity have highlighted positive associations between craving intensity and the strength of connectivity between the striatum and insula and between executive control networks and the amygdala in alcohol-dependent relapsers [26]. Temporal variation in craving has been investigated to explicate the increase of functional connectivity observed during abstinence [24,25]. For instance, significant positive correlations between levels of craving and connectivity at rest in the limbic network were found among abstinent smokers [27]. Further, relative to a satiated state, abstinent smokers showed both enhanced subjective craving and increased functional connectivity between frontal regions and other brain areas, including the hippocampus, visual and sensorimotor regions, the striatum and the cerebellum [28]. As highlighted in these studies, craving could indeed arise from a balanced communication between executive, limbic and interoceptive networks that could also be linked to its temporal fluctuations [29]. However, it has been suggested that intra-individual variability of cognitive processes, such as their temporal dynamic, could reveal new cerebral biomarkers that are not salient in its mean [30]. Hence, it has been proposed that extracting dynamic features from intensive longitudinal data to identify underlying cerebral substrates could result in high ecological validity and improve predictive capacity [31].

Herein, we aimed to exploit the complementarity of EMA and rs-fMRI to investigate the potential of craving dynamics as prognostic factors of use in individuals treated for Alcohol, Tobacco, and Cannabis Use Disorders on both behavioral and cerebral levels of processing. At the behavioral level, we hypothesized that indexes of craving dynamics could predict substance use within days beyond mean craving levels. To control for the directionality of this effect, *i.e.*, whether the craving dynamic predicts use and not the inverse relation, this analysis will be replicated at the momentary level. To do so we will analyze if craving absolute difference between successive time point influence later use while controlling for previous use earlier that day. On the cerebral level, we hypothesized that the craving dynamic would be significantly linked to intrinsic brain connectivity, itself representing a new marker of use risks. Hence, we conducted whole-brain exploratory analyses between rs functional connectivity and the mean craving dynamic in order to assess whether the strength of resulting connections could predict later substance use. As this is the first study linking resting state connectivity to index craving dynamics measured via EMA, this analysis will be conducted using a whole brain region-to-region (ROI-to-ROI) approach, which is widely used and produces unbiased, interpretable results [32]. To refine the spatial limitation of ROI-to-ROI results [33], we replicated our results using a seed-to-voxel approach. Finally, to examine the integrity of the rs functional networks that were characterized among the patients with SUD, we included a group of healthy subjects.

Methods

Participants

The present study was conducted in agreement with ethical standards depicted in the Helsinki Declaration and approved by the local ethical committee “Comité de Protection des Personnes de Sud-Ouest et Outre-Mer III» (N° 2014-A01668–39). Participants were volunteers and provided their written informed consent.

Patients were recruited between 2015 and 2018 in the context of their regular outpatient treatment for addiction at a university hospital and met DSM-5 criteria for a current alcohol, tobacco, or cannabis use disorder [34]. Patients received care, including pharmacotherapy and/or individual behavioral treatments (relapse prevention and psychosocial support). For the present study, patients with a history of bipolar disorder or schizophrenia (assessed via the Mini International Neuropsychiatric Interview 5.0.0 (MINI, [36]) were excluded, but patients with comorbid depression and / or anxiety were included. Addiction severity score for each patient was assessed with the Addiction Severity Index (ASI) [35] in their treated substance category. The experimental procedure started when patients were in the first month of treatment initiation.

Non-SUD participants were recruited through community announcements. They had no past or current psychiatric disorders, including substance abuse, as assessed by the MINI [36]. All participants had to be free from conditions incompatible with the use of a smartphone and were free of contraindications for MRI.

EMA procedure

The procedure is presented in Fig. 1. All participants were trained to operate a study-dedicated smartphone (Samsung Galaxy S with a 10.6 cm screen, 12-point font size). Subsequently, they were instructed to carry the smartphone with them for 7 consecutive days and to respond to five electronic surveys per day pseudo-randomly occurring including craving rating and substance use assessments. Pseudo-randomization was configured so that signals would occur between the participant's chosen "wake" and "sleep" hours. The resulting "day-time" intervals were then divided into 5 equal periods of time from which the first and last 23 min were deleted to ensure a minimum of 46 min in between assessments. Randomization was applied within each resulting time interval. Regarding craving evaluation, all participants had to rate the extent to which they currently felt "the urge or desire to use a substance" on a scale ranging from 1 (no desire) to 7 (extremely strong desire). To take into account multiple type of use, each use report was summarized by use of the primary substance during treatment (use of treated substance) and use of any substance.

The repeated craving assessments were summarized to index *within-day* variability (standard deviation), stability (auto correlation factor), and dynamic (Mean Successive Square Difference) and *between assessments* variability (absolute value of craving difference between each consecutive time point) as described in the statistical analysis section.

A subsample of patients and controls underwent one MRI session, including anatomical and resting-state imaging, within 48 h before initiating the EMA phase. Financial compensation was provided with 80€ in-store purchase vouchers for the completion of both the EMA and MRI phases of the study. Moreover, to maximize compliance rate, an additional store voucher of 20€ was offered to participants who completed at least 75 % of the assessments.

MRI acquisition

Brain imaging data were collected using a 3.0 Tesla GE 32-Channel Head Coil MRI system. Anatomical volumes were acquired using a sagittal 3D T1-weighted (Repetition Time = 8.5 ms, Echo Time = 3.2 ms, flip angle = 11°, FOV = 256 mm × 256 mm, voxel size = 1 mm^3, 176 slices). The resting-state functional images were collected using a single-shot echo-planar sequence (RT = 2.2 s, ET = 27 ms, flip angle = 80°, FOV = 192 mm × 192 mm, voxel size = 3 mm × 3 mm × 3.5 mm, 42 axial slices, total duration 10.07 mn), during which participants were instructed to keep their eyes closed, not to fall asleep, and not to think about anything in particular.

Preprocessing

Preprocessing steps included use of FMRIPREP [37]. T1- weighted (T1w) images were corrected for non-uniformity using ANTs N4Bias-FieldCorrection v2.1.0 [38] and skull-stripped using ANTs ants-BrainExtraction v2.1.0 (using the OASIS template). These T1w images were then normalized to the ICBM 152 Nonlinear Asymmetrical template version 2009c [39] via nonlinear registration with the antsRegistration tool (ANTs v2.1.0 [40], using brain-extracted versions of both T1w volumes and the template, which produced images that were segmented using fast[50] FSL v5.0 [41]. Functional images underwent slice timing

correction using 3dTshift from AFNI v16.2.07 [42], motion-correction via mcflirt (FSL v5.0.9, [43] and distortion correction through an implementation of the TOPUP technique [44] using 3dQwarp (AFNI v16.2.07 [42]. Images were then co-registered to the T1w using boundary-based registration [45] with nine degrees of freedom in FSL flirt. Motion correcting transformations, field distortion correcting warp, BOLD-to-T1w transformation, and T1w-to-template (MNI) warp were concatenated and applied in a single step using antsApplyTransforms (ANTs v2.1.0). After correction for six motion parameters, white matter and CSF mean signals were removed with regression analysis using a general linear model (GLM), and ICA-based Automatic Removal Of Motion Artifacts (AROMA) was used to generate aggressive noise regressors to further reduce motion-artefact [46]. Finally, denoised data were bandpass filtered (0.008–0.1 Hz). The BOLD data were not subjected to spatial smoothing [47].

All MRIs were inspected by a radiologist. Participants with evidence of potential brain structural abnormalities were excluded (four control subjects and two patients). Further, two patients with movements >3 mm during the rs fMRI acquisition were excluded from the fMRI analyses solely.

Functional connectivity analyses were conducted using the CONN.16 toolbox [48] implemented in SPM12 software (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) on MATLAB, version 12.0 (http://www.mathworks.fr/products/matlab). Correction for multiple comparisons used FDR, and effects were considered significant at $p < 0.05$.

Whole brain ROI to ROI functional connectivity

For each subject in the MRI subsample, the AAL atlas 3 [49] was used to build the ROI functional connectivity maps. The choice of this atlas was driven by the wide use of this atlas in neuroimaging research, including in activation and resting state studies, to allow the comparison of our results to a large pool of studies. To limit partial volume effects, each ROI was restricted to voxels belonging to an estimated gray-matter mask derived from the T1w image segmentation.

Mean fMRI time-series were extracted within each ROI. Functional connectivity was estimated using Pearson's correlation coefficients between the BOLD time courses of all ROI pairs. These correlation coefficients were Fisher Z-transformed to produce a 166 × 166 matrix representing the intensities of brain functional connections among the 166 ROIs.

Seed to voxel functional connectivity

For each of the significant connections between two ROIs, a seed-to-voxel analysis was conducted to identify the spatial localization of significant voxels. Connectivity was computed using Fisher Z-transformed correlation coefficients between the ROI BOLD time courses and each whole-brain individual voxel BOLD time-series.

Statistical analyses

For maximal statistical power, behavioral analyses were conducted including all participants that completed the EMA phase. Compliance rates with the EMA were defined as the percent

of completed surveys during the whole week and were calculated for description purposes. For each group, we calculated the mean level, standard deviation (SD), within-person autocorrelation (ACF) and Mean Square Successive Difference (MSSD) of craving per day resulting in 7 repeated measures per individual. Equations for each variability index are presented in the Supplementary Table 2. To evaluate substance use, we summed the number of times per day each individual used any substance or the treated substance.

To control for confounding effects of previous levels of craving and substance use on the links between craving dynamic and substance use, we also characterized craving fluctuations between time assessments and conducted prospective analyses. For this analysis, we calculated the absolute value of craving difference between each consecutive time point within days to predict the probability of later use.

Group comparisons

Due to the non-normality of the data distribution, group comparisons for mean craving, SD craving, MSSD craving, ACF craving, and substance use were performed using nonparametric tests: Mann-Whitney tests for the group effect (patients versus controls); one-way Kruskal-Wallis (nonparametric) ANOVA, and post-hoc Dwass-Steel-Critchlow-Fligner (DSCF) pairwise comparisons for the effect of SUD subgroups (alcohol, tobacco, cannabis).

Hierarchical modeling of craving dynamics

In the SUD group of the EMA sample, we used hierarchical linear and nonlinear modeling (HLM version 8.0; [50] to account for the specific variance of repeated within-person first-level (at the day level) variables (craving MSSD or SD craving or ACF craving, mean craving, and substance use per day) nested into between-person second level variables (clinical and demographical). In each model, control and independent variables were entered as fixed effects; random effects on the first level intercepts equations were added. First-level continuous predictors were centered around the participant's own level; second-level continuous predictors were centered around the group mean. Dichotomous predictors for each level were entered uncentered.

For day-level analysis, the number of substance use occasions was entered in the model as outcomes, with craving dynamics indexes and mean craving of the same day as predictors, with age, sex, and addiction severity as control variables. The γ-coefficients generated represent the average within-person association between a predictor (e.g., MSSD) and the outcome (e.g., daily substance use).

For the prospective analyses (at the assessment moment level) in the SUD group, we entered absolute difference in craving between t and $t + 1$ as predictors of subsequent substance use (measured at time $t + 2$) while controlling for previous substance use (measured at $t + 1$), with age, sex, and addiction severity as second-level control variables.

Missing data at each level were excluded from the analysis: if missing data were located at the first level, the data from that day would be discarded from the analysis. No missing data were found in the second-level variables.

Whole brain ROI-to-ROI functional connectivity

To assess resting-state connections related to craving instability in the SUD group of the MRI subsample, we employed user-defined contrasts in the Conn Toolbox, with MSSD craving as the between-subject variable and connectivity strength as the outcome variable. Results were corrected for multiple comparisons using FDR with an alpha level of 0.05. The strength of connections in the identified connections was then extracted in the two groups (SUD and controls) for comparison.

The connectivity data were normally distributed, allowing for use of parametric analyses. Within the SUD group, we also compared sex, comorbidity, and type of substances using independent sample *t*-tests and ANOVAs.

Finally, due to the non-normality of the distribution within the psychological data, Spearman correlations were used to assess relationships between identified connectivity strength and the sum of substance use occasions during the week for any substance and for the treated substances. Analyses were performed using JAMOVI software version 1.2 (https://www.jamovi.org), two-sided, and considered significant when $p \leq 0.05$.

Seed-to-voxel analyses were conducted using each significant ROI as a seed and MSSD craving as between-subject variables. Once again, results were corrected for multiple comparisons using FDR with an alpha level of 0.05.

Results

Descriptive analyses

The behavioral analyses were based on the EMA sample, composed of 99 participants. The SUD group comprised 64 patients (33 men; mean age 41.66 ± 11.81; mean compliance 86 %, mean addiction severity 6.45), including 32 treated for alcohol, 20 for tobacco, and 12 for cannabis. The control group included 35 participants (18 men; mean age 34 ± 8.22; mean compliance 94.29 %). See Table 1 for descriptive and comparison statistics.

In the MRI subsample, 74 participants were included, with 40 SUD patients (20 men; mean age 42.42 ± 11.34; mean compliance 86.29 %, mean addiction severity 6.52), including 20 treated for alcohol, 13 for tobacco, and 7 for cannabis misuse. The control group included 34 participants (18 men; mean age 34.26 ± 8.19; mean compliance 94.29 %). See Supplementary Table 1 for descriptive and comparison statistics.

Craving dynamics in the EMA sample with SUD

Hierarchical linear and nonlinear modeling in the SUD group—These analyses did not reveal any significant effect of within-day variability of craving (SD) or craving inertia (ACF) on substance use for any substance or for the treated substances while controlling for mean craving, age, sex, and addiction severity. However, we found an impact of the third craving dynamic index. While controlling for mean craving, age, sex, and addiction severity, within-day instability of craving (MSSD) significantly predicted daily use of the treated substance. This effect was not found using the use of any substance during the same day as an outcome. These analyses also revealed significant interindividual differences, whereby

craving instability was linked to greater substance use in men than women. These results are highlighted in Table 2.a.

As noted in Table 2.b. the prospective analyses indicated that the absolute difference of craving between t and $t + 1$ significantly predicted the use of any substance at $t + 2$ while controlling for previous craving level (at $t + 1$), previous use of any substance, age, sex, and addiction severity, such that greater momentary variability was linked to greater probability of subsequent use. Sex differences indicated greater variability in men than women. However, the momentary absolute difference in craving was not associated with the subsequent use of the treated substances (at $t + 2$) while controlling for craving level, use of the treated substances at $t + 1$, age, sex, and addiction severity.

Neuroimaging results

ROI-to-ROI connectivity—As displayed in Fig. 2, in the SUD group, craving instability (MSSD) was associated with connectivity strength in five pairs of areas. A positive association (that is, greater instability correlated with stronger connectivity) involved the functional connection between the left anterior cingulate cortex and the right thalamus. Negative associations were found for functional connections between the right thalamus and the cerebellum (vermis 10), right thalamus and left rolandic cortex, right thalamus and left heschl gyrus, and between left heschl gyrus and left inferior orbital frontal cortex.

Seed-to-voxel connectivity—In the SUD group, voxels that were significantly connected to the different seeds and for which connectivity strength was correlated to craving instability are presented in Table 3. The main highlights from this analysis identified additional clusters located in the insula and in the precuneus.

Associations of connectivity strength with clinical variables—The strength of functional connectivity differed between controls and SUD patients within one connection only. The connectivity between the cerebellar vermis 10 and the right thalamus PuL was significantly weaker in the SUD group than in the controls ($T = 5.206$, $p < 0.001$, *Cohen's d = 1.21*). Weaker vermis-thalamus connectivity correlated with greater amount of use of any substance in the week in the overall sample ($rho = -0.546$, $p < 0.001$).

In the SUD group, in contrast with the cerebellar-based relations, connectivity strength between the left anterior cingulate cortex and the right thalamus was positively correlated with the amount of use of the treated substances ($rho = 0.443$, $p = 0.004$). In this group, there was no effect of sex or SUD subgroup on connectivity strength.

Discussion

The present study is the first to have investigated the dynamics of substance craving in real life and real time in association with neural correlates at rest that served as prognostic factors of future substance use in patients in treatment. This effort characterized the fluctuations of craving by assessing their impact on the use of different substances both within each day and within prospective occasions using several temporal indexes, thereby extending the current literature [20,21].

Within days, EMA data permitted the computation of craving variability (SD), inertia (ACF), instability (MSSD), mean craving, and substance use (any substance or treated substances). Mean craving level was higher in the cannabis group than in the alcohol group. This result is not new, as differences between SUD groups have been found previously for cue-induced [51], self-reported [52], or even EMA-assessed [17] craving, with generally the lowest level of craving associated with alcohol. Yet, the SUD group did not exhibit significant effects in overall craving dynamics moderated by the type of treated substance. Whereas craving intensity depended on the type of substance used, its dynamic pattern may have arisen from a general process of addiction. The clinical significance of these findings could be of primary importance, suggesting that a potential prognostic factor, craving instability, could be similarly targeted regardless of the subtype of substance use disorder. This study being the first to characterize and compare the dynamic of craving in different types of SUD in the context of identified functional brain systems requires replication.

Regarding the association between craving dynamics and substance use, the higher the craving instability (MSSD), the more the patients tended to use the substance they were treated for independently from their mean level of craving. This finding comports with the previously highlighted link between craving instability and opioid substance use [21]. Nonetheless, we failed to observe any significant effects for the other measures of craving dynamics, namely, standard deviation – which indexes craving variability - or autocorrelation factor – which indexes craving inertia -, even though craving inertia has been linked to substance use in patients with an opioid use disorder [21] and craving variability to substance use in both opioid and tobacco use disorders [18, 19]. It may be premature to conclude that the other indexes of craving dynamic are irrelevant, but the present findings suggest that taking variability and temporal dependency into account simultaneously using measures like MSSD allows a fine-grain, sensitive characterization of craving dynamic. If within-days analyses do not inform the temporality or causality that can exist between craving instability and substance use, one of the strengths of EMA surveys is its ability to investigate the temporal lag on the influence of one variable on the other. Using this approach, the investigation of prospective links within occasions highlighted that momentary absolute changes in craving predicted substance use independently from craving intensity and previous substance use, such that the greater the differences between the two time-points, the higher the risk of later substance use. To the best of our knowledge, this is the first study suggesting that instability in craving may be a trigger for use in several SUD types, beyond the known effect of craving intensity.

Another novelty of the present study is the investigation of the functional cerebral correlates of craving dynamics. Here, we revealed that the connectivity strength between the left anterior cingulate cortex (ACC) and the right thalamus in the SUD group was related to greater instability of the craving experience. Conversely, the weaker the level of functional connectivity between the left Heschl gyrus and left inferior orbitofrontal cortex, between the left Heschl gyrus and the left Rolandic area, and between the right thalamus and the cerebellum, the greater the craving instability. The refinement of these results using a seed-to-voxel approach allowed further specification of functionally connected areas and revealed an additional cluster in the insula, as well as other areas already identified in

craving-related studies as reported in a meta-analysis [53]. In addition, the present results are consistent with earlier findings in SUD where craving was observed to arise from an imbalance between the executive, limbic, and interoceptive cerebral systems that are constantly interacting [29]. In the theoretical metacognitive hub model of SUD [8], the first component of craving, which is the automatic system relying on the limbic system, would trigger substance use through invoking first line, automatic responses based on associative learning. The second component, the executive system mostly involving frontal regions, would be able to regulate this signal by employing cognitive, deliberate control. The third component is the interoceptive component and would involve the insula acting as a mediator between the other two dynamic components by integrating an interoceptive signal and enhancing the impulsive system, disrupting the controlled response, thus emphasizing motivation towards the substance [8]. Thus, consistent with previous findings and emerging models of addiction, the brain systems identified in the present study may add evidence for SUD-related intrinsic connectivity changes in 1/ executive functioning sustained by the orbitofrontal cortex [54], the superior frontal cortex [55], and the central opercular cortex [56]; in 2/ automatic processes involving limbic areas such as the anterior cingulate cortex [57], the thalamus [58] and 3/ interoception mechanisms mediated by the insula [8,59], and the precuneus [60].

MSSD has been extensively used in emotion research as an index of instability (of mood or affect, for example) arising from a deficit of regulation, and hence less control over large shifts or fluctuations [61]. The sources of such instability could be numerous, from psychological [8] to biological process of circadian rhythms [62]. Based on our findings, we suggest that dysfunction of selective brain connections could at least partially underlie deficits in craving regulation and thus promote use. This effect was found even in patients beginning treatment but, as demonstrated in our descriptive analysis and by our prediction of use, have failed to abstain. Specifically, two of the five pairs of brain regions linked to craving instability could be interpreted to constitute prognostic factors of substance use. Indeed, not only was cerebello-thalamic connectivity strength greater in the controls than the SUD group, but additionally, weaker connectivity was associated with more frequent substance use occasions within the week in the overall sample. Moreover, the stronger the connectivity between the anterior cingulate cortex and the thalamus, the greater the number of treated substance use occasions within SUD patients. If our results regarding intrinsic connectivity group differences and their link with craving variability are confirmed, these links would argue for targeting such areas in SUD treatments.

Limitations

Our study examined sex differences that seem to moderate the impact of risk factors of use, although our goal was not to identify sex-specific predictors of use, challenged by small sample sizes. Thus future studies are needed to elucidate sex risk factors in SUD populations. Secondly, as we highlighted craving dynamics as a potential clinical indicator, no study yet has investigated the impact of pharmacological or psychological treatment on such measures. Further investigations are thus needed to test the pertinence of targeting dynamics as a clinical outcome. These dynamics were calculated based on random assessments of their current level. Whereas assessing current craving level repeatedly

and closely over time to use has been recommended [63] future studies should consider replicating our findings using different self-report methods. Concerning cerebral substrates of craving dynamics, our analysis was conducted using a ROIs approach and could be completed by an analysis of larger scale networks subserving its-fluctuations. Finally, it should be noted that our population was restricted to patients already undergoing treatment. As we did not assess potential treatment effects, further studies are needed to clarify the impact of treatment strategy on craving dynamics or potential "rebound" effect of craving that could emerge from the abstinence attempts [64].

Conclusion

Replication of the present findings on craving instability and its underlying neural substrates as prognostic factors of substance use could lead to new smartphone-based applications in the context of personalized medicine. Indeed, daily assessed craving dynamics during the therapeutic process could identify temporal patterns of use by high-risk SUD patients whether or not in treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Data availability

Data will be made available on request.

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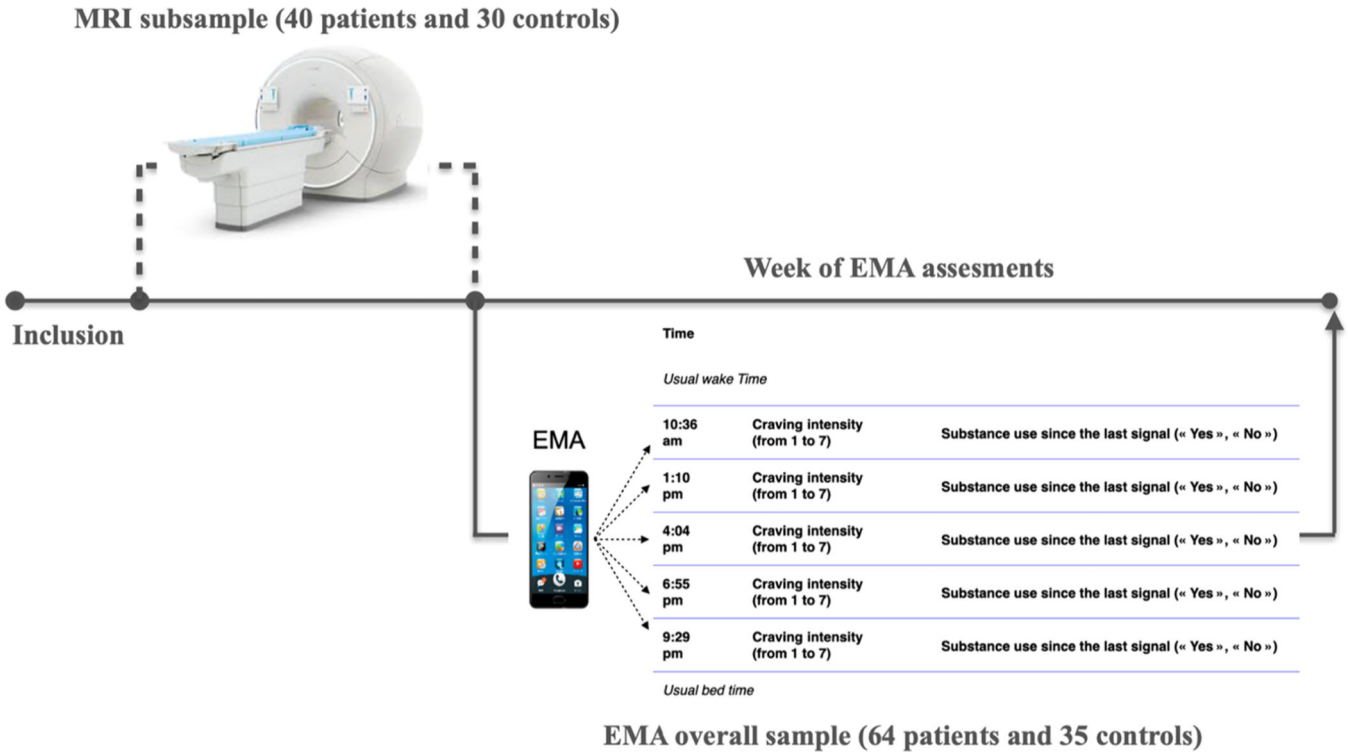

Fig. 1. Overall methodology for the EMA sample and MRI subsample.

Legend: All participants underwent an interview to assess inclusion criteria, including the Mini International Neuropsychiatric Interview and the Addiction Severity Index for the patients. All participants underwent a week of EMA assessments. Usual “wake” and “sleep” times were selected by each participant to ensure that they would be able to answer each test signal. Typical day of EMA is represented above and included signals occurring randomly within 5-time intervals periods. At each signal, craving was assessed on a scale from 1 to 7, and Substance use was coded in a dichotomous manner (“Yes” or “No”) for the substance they are treated for and for any substance. These within day assessments were then extracted to summarize craving variability (Standard Deviation), inertia (Auto Correlation Factor), instability (Mean Successive Square Difference) and number of Substance Use occasions for each day. A subsample of these participants also underwent MRI acquisition, including a resting state session, prior to the EMA phase.

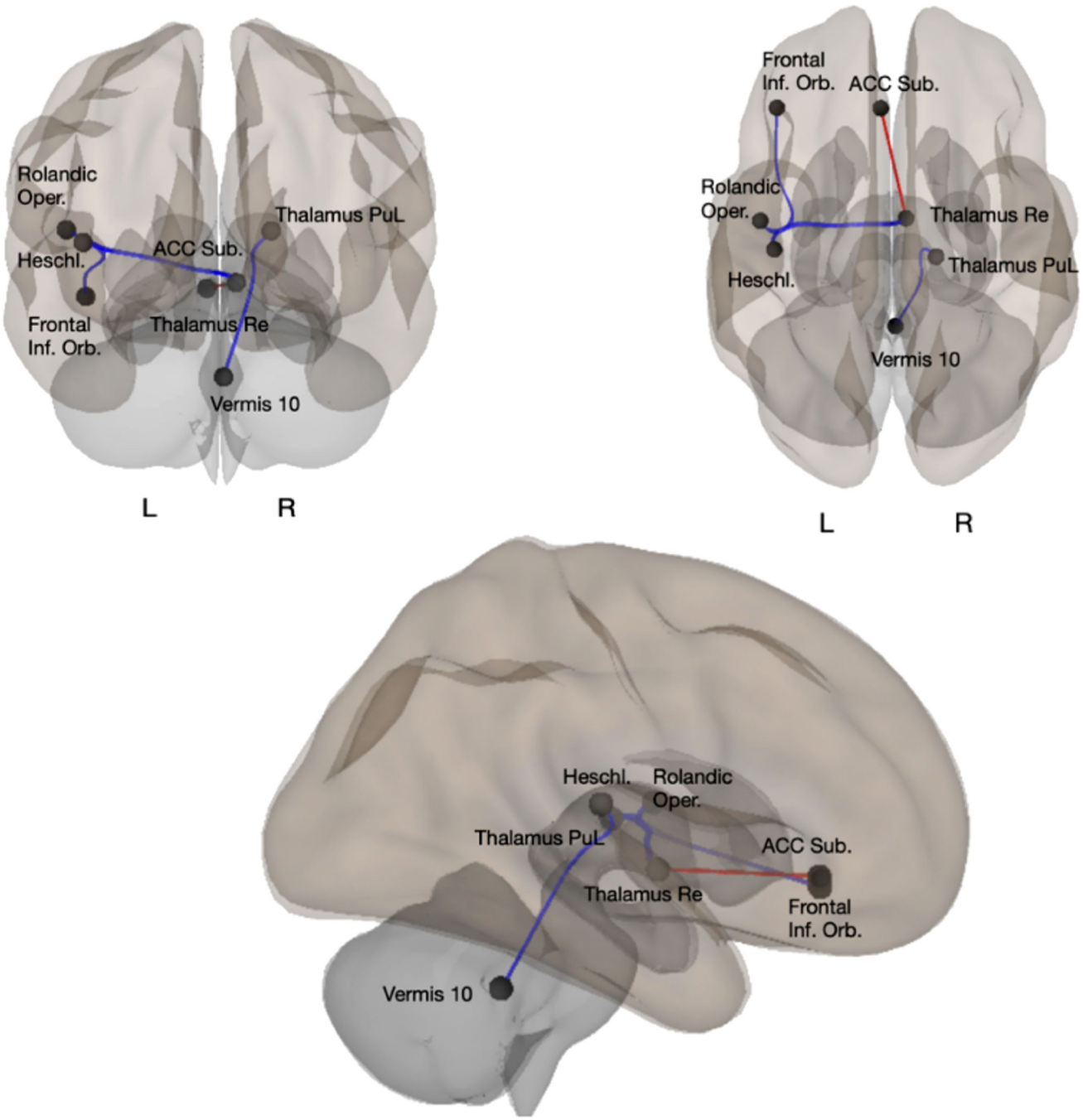

Fig. 2. Resting state connections correlating negatively (in blue) and positively (in red) with craving instability

L: Left; R: Right; Oper: Opercular; Inf: Inferior; Orb: Orbital; ACC: Anterior Cingulate Cortex, Re: Reuniens, PuL: Pulvinar Lateral, Rs: resting state

Legend: Regression analyses were conducted within the CONN toolbox between the individual connectomes and mean MSSD craving from each patient with SUD in the MRI subsample correcting for false discovery rate (FDR) with alpha level of 0.05. Resulting connections are highlighted in the above figure and colored depending on their association with MSSD craving, negatively (highlighted in blue) or positively (highlighted in red). The

strength of connectivity within these connections was then extracted for both patients with SUD and controls to be compared across both groups and conduct correlations analysis with the number of substance use occasions during the week.

Table 1

Descriptive statistics of the behavioral and psychological variables of interest in the overall EMA sample ($n = 99$).

	Healthy Control ($N = 35$)			**Any Addiction ($N = 64$)**			**Alcohol ($N = 32$)**			**Tobacco ($N = 20$)**			**Cannabis ($N = 12$)**		
	M	SD	%	M	SD	%	M	SD	%	M	SD	%	M	SD	%
Age	34.00 *	8.22		41.66	11.81		44.20 *B*	11.30		43.40 *C*	11.10		32.00	10.20	
Sex (% male)			51.42			51.56			62.50 *B*			20.00 *C*			81.81
Education (years)	14.40	2.91		13.40	2.52		13.10	2.24		14.40	2.70		12.60	2.57	
Depression Comorbidity			–			17.18			21.87			5.00			27.27
Anxiety Comorbidity			–			28.10			21.87			20.00			58.33
EMA Compliance (%)			94.29 ***			86.00			87.43			86.00			83.43
Addiction Severity	–	–		6.52	0.73		6.53	0.76		6.45	0.76		6.58	0.67	
Mean craving	1.02 ***	0.10		2.85	1.46		2.51 *B*	0.971		2.87	1.40		3.73	1.47	
MSSD craving	0.07 ***	0.60		2.81	4.39		2.70	2.92		3.32	4.46		2.62	1.06	
SD craving	0.03 ***	0.08		1.60	0.56		1.03	0.59		1.00	0.60		1.26	0.37	
ACF craving	0.98 ***	0.14		0.03	0.56		0.06	0.59		0.02	0.55		−0.02	0.47	
Use of any substance (per day)	0.28 ***	0.61		3.20	1.58		3.48	1.52		2.89	1.61		2.98	1.54	
Use of treated substance (per day)	–	–		1.98	1.66		1.52 *A*	1.53		2.73	1.62		1.92	1.62	

S.D.: standard deviation; M: Mean; ACF: Auto Correlation Factor, MSSD: Mean Successive Square Differences; Min: minimum; Max.: maximum ;

*: <0.05;

**< 0.01 ;

***<0.001 ;

A: Alcohol ≠ Tobacco ;

B: Alcohol ≠ Cannabis ;

*C*Tobacco ≠ Cannabis.

Table 2a

Associations of MSSD craving and use of any substance while adjusting for age, sex and addiction severity in the EMA sample with SUD.

Variable	Use of Any Substance				Use of Treated Substance			
	γ	SE	df	T ratio	γ	SE	df	T ratio
Within-person associations								
Mean Craving	0.063	0.258	60	0.245	0.100	0.239	60	0.676
MSSD Craving	0.039	0.084	60	0.465	0.145	0.069	60	2.116*
Between-person moderators								
Age	0.002	0.002	60	0.935	−0.001	0.001	60	−0.031
Sex	−0.038	0.047	60	−0.805	−0.082	0.038	60	−2.180*
Addiction Severity	0.031	0.031	60	1.003	0.004	0.018	60	0.255

MSSD: Mean Successive Square Differences;

*$p < 0.05$.

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Table 2b

Associations of momentary craving absolute difference and use of any substance while adjusting for age, sex and addiction severity in the EMA sample with SUD.

Variable	Use of Any Substance				Use of Treated Substance			
	γ	SE	df	T ratio	γ	SE	df	T ratio
Within-person associations								
Previous craving	0.296	0.153	60	1.939	0.192	0.168	60	1.143
Previous use	0.568	0.663	60	0.856	0.385	0.558	60	0.690
Craving absolute differences	0.218 **	0.082	60	2.646	0.171	0.113.	60	1.513
Between-person moderators								
Age	−0.002	0.003	60	−0.513	−0.002	0.004	60	−0.679
Sex	−0.156	0.057	60	−2.725 **	−0.121	0.074	60	−1.631
Addiction Severity	0.041	0.048	60	0.841	0.037	0.057	60	0.641

** $p < 0.01$.

Table 3

Results of the seed-to-voxel analysis.

Seed		Peak coordinates			Size (Nb Voxels)	P FDR
		x	y	z		
Frontal Inf. Orb. L						
	Not labeled	00	−28	+18	32	0.003905
	Heschl's L / Insula	−38	−22	+08	27	0.006320
Heschl L.	Sup. Temporal post L.	−70	−28	+04	18	0.042885
	Frontal inf. orb. L.	−42	+28	−08	56	0.000024
	Insula L.	−40	+10	−06	41	0.000239
	Cereb. 9 L.	−12	−38	−48	27	0.003691
Vermis 10	Not labeled	−24	+40	+02	21	0.012526
	Sup. Frontal L. / R.	+02	+38	+46	83	0.000000
	Intracalcarine L.	−16	−72	+08	48	0.000058
	Intracalcarine R.	+10	−72	+06	24	0.008560
	Precuneus	+20	−60	+12	21	0.014059
Thalamus *Re* R.	Precuneus	−22	−56	+08	16	0.045429
	Central opercular L. / Heschl's L.	−40	−20	+14	53	0.000011
	Central opercular R. / Insula R.	+44	−02	+12	28	0.002143
	Thalamus R.	+12	−24	+18	20	0.013721
	Fusiform L.	−22	−54	−12	18	0.015154
	Brain stem	−16	−24	−42	18	0.015154
	Precentral R.	+50	−10	+60	15	0.032970
	Sup. Frontal R.	+04	+20	+60	13	0.042471
	Cingulate ant.	+04	+44	+14	13	0.042471
	Brain stem	+06	−24	−48	13	0.042471
	Insula L.	−36	−24	+04	12	0.042471
	Lateral occipital inf. R.	+42	−72	−10	12	0.042471
	Fusiform R.	+32	−36	−16	12	0.042471
Thalamus PuL R.	Brain stem	−10	−30	−44	12	0.042471
	Not labeled	−26	−32	+00	20	0.022962

Seed		Peak coordinates			Size (Nb Voxels)	P FDR
		x	y	z		
Anterior cingulate cortex	Brain stem / Cereb. 9 L.	+00	−46	−52	19	0.022962
	Temporoccipital R.	+62	−50	−02	16	0.037509
	Not labeled	−34	−44	+12	15	0.038391
	Middle temporal post. R.	+70	−38	−12	14	0.042207
	Brain stem / Cereb. 10 L.	−14	−28	−42	171	0.000000
	Cereb. 9 R.	+04	−48	−48	87	0.000000
	Brain stem	+00	−36	−54	26	0.003826
	Supramarginal post .L.	−64	−40	+12	19	0.018781
	Parahippocampus post. L.	−22	−22	−26	18	0.019999
	Cingulate ant.	+10	+00	+40	15	0.034847
	Parahippocampus post. R.	+20	−24	−24	15	0.034847
	Central opercular L.	−48	+04	+12	14	0.036960
	Brain stem / Cereb. Vermis 10	−06	−40	−24	14	0.036960

L.: Left; R: Right; Inf.: Inferior; Sup: Superior; Ant: Anterior; Post: Posterior; Cereb: Cerebellum.