



Craving : an early and predictive marker of tobacco, alcohol and cannabis addiction

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THÈSE PRÉSENTÉE
POUR OBTENIR LE GRADE DE

**DOCTEUR DE
L'UNIVERSITÉ DE BORDEAUX**

ÉCOLE DOCTORALE SCIENCES DE LA VIE ET DE LA SANTÉ
SPÉCIALITÉ NEUROSCIENCES

Par Emmanuelle BAILLET

**Le craving : un marqueur précoce et prédictif de l'addiction
au tabac, à l'alcool et au cannabis ?**

Sous la direction de : Marc AURIACOMBE

Soutenue le 5 décembre 2023

Membres du jury :

M. AURIACOMBE Marc	Professeur	Univ. Bordeaux	Directeur
M. BROUSSE Georges	Professeur	Univ. Clermont Auvergne	Président
Mme CHILDRESS Anna-Rose	Professeure	Univ. Pennsylvanie	Rapportrice
M. AHMED Serge	Dir. Recherche	Univ. Bordeaux	Examineur
Mme CHANRAUD Sandra	Ens-chercheuse	Univ. Bordeaux	Examinatrice
Mme KOBAN Léonie	Chercheuse	Univ. Lyon	Examinatrice

Membres invités :

Mme KERVRAN Charlotte	Ingé. De Recherche	Univ. Bordeaux	Invitée
M. SI-MOHAMMED Hakim	MCU	Univ. Lille	Invité

Le craving : un marqueur précoce et prédictif de l'addiction ?

RÉSUMÉ

Introduction : L'addiction, ou trouble de l'usage (TU), est caractérisé par une dérégulation du contrôle de l'usage de substances renforçantes qui se traduit par la persistance de l'usage en dépit des conséquences négatives. Le craving, défini comme une envie irrésistible de consommer, est à la fois un critère diagnostique parmi les 11 critères du DSM-5 et un phénomène fluctuant dont les variations journalières en vie quotidienne explorées avec la méthode Ecological Momentary Assessment (EMA) ont été prospectivement associées à l'usage, lui donnant ainsi une valeur pronostique et étiologique potentielle. La présence du craving chez des sujets avec une addiction légère suggère qu'il pourrait être un marqueur précoce. Par ailleurs, si le craving est un puissant prédicteur d'usage et de rechute, à court et moyen terme (1 an), l'impact à long terme (5 ans et plus) de ses fluctuations est inconnu. Le paradigme de réactivité aux cues entraînerait à la fois du craving et des modifications de l'activité cérébrale et autonome, suggérant que ces changements pourraient constituer l'expression physiologique du craving. *Le but de cette thèse était d'étudier le rôle du craving dans le développement de l'addiction ; son impact sur la rechute à long terme et ses corrélats physiologiques.*

Méthode : Un total de 1528 sujets présentant une addiction ou un usage de différentes substances, en soin ou hors soin ont été inclus dans différents protocoles. Le craving a été évalué soit en tant que critère diagnostique (un trait, présence ou absence), soit en tant que phénomène fluctuant (un état, intensité variable). Les critères diagnostiques du DSM-5 ont permis d'établir un réseau de symptômes chez des patients en traitement et d'explorer le rôle prédictif du craving sur l'addiction dans une étude longitudinale en population générale. L'EMA a permis la récolte du craving et un capteur portable la collection de données physiologiques en vie quotidienne pendant 14 jours. Des modèles multiniveaux ont examiné les fluctuations du craving et son impact sur la sévérité et la rechute ; puis des algorithmes de machine learning nous a permis d'explorer ses corrélats physiologiques.

Résultats : Nos résultats montrent, pour différentes substances, que le craving était le critère le plus central dans les analyses en réseau et qu'une relation dose-réponse du craving et de sa persistance pendant 12 mois était associée au nombre de critères diagnostiques d'addiction présents. De manière dynamique, les variations d'intensité du craving pendant les 14 premiers jours de traitement montraient une diminution plus lente pour les personnes en rechute de l'addiction à plus de 5 ans. Enfin, nous avons pu établir un pattern physiologique capable de distinguer le craving du non-craving.

Conclusion : Dans cette thèse, nous confirmons la place majeure du craving dans l'addiction en tant que critère central de l'expression de l'addiction et nous mettons en évidence qu'il est un critère précoce et prédictif dans le développement et la sévérité de celle-ci. Nous montrons que les fluctuations d'intensité du craving en début de traitement pourraient constituer un marqueur prédictif de rechute à long terme, c'est-à-dire de réponse au traitement à long terme et qu'un pattern physiologique permettait de distinguer le craving du non-craving en vie quotidienne. Ces résultats soulignent que le craving pourrait constituer un marqueur de l'addiction et ouvre la voie des biomarqueurs du craving, offrant de nouvelles perspectives sur ses mécanismes sous-jacents et de nouvelles méthodes de repérage et de traitement.

Mots clés : Craving ; Addiction ; Évaluation momentanée écologique ; Biomarqueurs ; Détection précoce

Craving: an early and predictive marker of addiction?

ABSTRACT

Introduction: Addiction, or substance use disorder (SUD), can be characterized by deregulation of control over the use of reinforcing substances, resulting in persistent use despite negative consequences. Craving, defined as an intense urge to use, is both a diagnostic criterion among the 11 DSM-5 criteria and a fluctuating phenomenon whose daily variations in everyday life explored with the Ecological Momentary Assessment (EMA) method have been prospectively associated with use, giving it a potential prognostic and etiological value. The presence of craving in subjects with mild addiction suggests that it could be an early marker. On the other hand, while craving is a powerful predictor of use and relapse in the short and medium term (1 year), the long-term impact (5 years and more) of its fluctuations is unknown. The cue-reactivity paradigm would lead to both craving and changes in brain and autonomic activity, suggesting that these changes could be the physiological expression of craving. The aim of this PhD project was to investigate the role of craving in the development of addiction, its impact on long-term relapse and its physiological correlates.

Method: A total of 1,528 subjects with addiction or use of different substances, in or out of treatment, were included in different protocols. Craving was assessed either as a diagnostic criterion (a trait, presence or absence), or as a fluctuating phenomenon (a state, of variable intensity). DSM-5 diagnostic criteria were used to establish a network of symptoms in patients requesting treatment, and to explore the predictive role of craving on addiction in a longitudinal general population study. The EMA was used to collect craving data, while a wearable sensor was used to collect physiological data over a 14-day period. Multilevel models examined craving fluctuations and their impact on severity and relapse; then machine learning algorithms enabled exploration of its physiological correlates.

Results: Our results show that, for different substances, craving was the most central criterion in the network analyses, and that a dose-response relationship for craving and its persistence over 12 months was associated with the number of SUD diagnostic criteria present. Dynamically, variations in craving intensity during the first 14 days of treatment showed a slower decline for people relapsing to addiction after 5 years or more. Finally, we were able to establish a physiological pattern distinguishing craving from no-craving episodes.

Conclusion: In this PhD project, we confirm the major role of craving as a central criterion for the expression of addiction, and document that it is an early and predictive criterion in the development and severity of addiction. We show that fluctuations in craving intensity at the start of treatment could be a predictive marker of long-term relapse, i.e., long-term response to treatment, and that a physiological pattern could distinguish craving from no-craving episodes in daily life. These results underline the potential of craving as a marker of addiction and pave the way for biomarkers of craving, offering new insights into its underlying mechanisms and new methods of identification and treatment.

Keywords: Craving; Addiction; Ecological Momentary Assessment; Biomarkers; Early Detection

Le craving : un marqueur précoce et prédictif de l'addiction ?

RÉSUMÉ VULGARISÉ

Le craving, une envie irrépressible de consommer, jouerait un rôle déterminant dans l'addiction. Le but de cette thèse était de mieux le caractériser. En utilisant différentes méthodes chez des personnes avec addiction et en traitement et des consommateurs non traités, nous avons montré que la présence du craving était associée à plus de risque d'avoir une addiction sévère suggérant que le craving était parmi les premiers critères à apparaître. Nous avons aussi montré que l'importance de la diminution du craving en début de traitement était associée à plus de rechutes 5 ans plus tard. Enfin, en utilisant des capteurs physiologiques en vie quotidienne, nous avons pu établir un pattern physiologique capable de repérer les épisodes de craving. Ces résultats ouvrent des possibilités pour mieux comprendre les mécanismes physiologiques de l'addiction et la possibilité de nouvelles méthodes thérapeutiques adaptable à chaque individu.

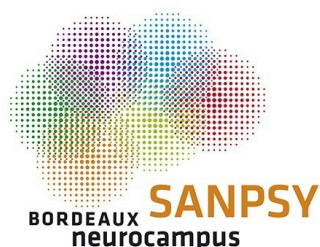
Craving: an early and predictive marker of addiction?

POPULARIZED SUMMARY

Craving, an intense urge to use, is thought to play a key role in addiction. The aim of this PhD project was to better characterize craving. Using a variety of methods, we showed that the presence of craving was associated with an increased risk of severe addiction, suggesting that craving was one of the first criterion to appear. We also showed that the intensity of craving reduction at the start of treatment was associated with more relapses 5 years later. Finally, by using physiological sensors in daily life, we were able to establish a physiological pattern identifying craving episodes. These results open up possibilities for a better understanding of the physiological mechanisms of addiction, and the possibility of new individualized treatment methods.

RESEARCH UNIT

This PhD work was conducted **within the Addiction Team at Sanpsy Lab, University of Bordeaux, Bordeaux, France.**



Bordeaux Neurocampus, Unité Sommeil, Addiction et Neuropsychiatrie – UMR 6033 SANPSY, Université de Bordeaux, France

Équipe Phénoménologie et déterminant des comportements appétitifs

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Funding of the PhD:



This PhD work lasted 3 years (01/01/2021 – 31/12/2023) and was funded by a doctoral PhD grant by French Institute of Health (Institut National du Cancer & Institut de Recherche en Santé Publique – INCa-IReSP_15746) following a call for doctoral grant applications: "Fighting against psychoactive substance use and addictions" ([AAP/INCA/INRESP/SPADOC](#)). The research program related to this PhD project received financial support from the French government in the framework of the University of Bordeaux's IdEx "Investments for the Future" program/GPR BRAIN_2030 (Adapsy project). Funding for the EMA study was provided by Research Grant AAP-19-ADDICTIONS-16 from the public health research institute (IReSP) and Aviesan Alliance as part of the call for research projects to combat addiction to psychoactive substances to Marc Auriacombe and Fuschia Serre. Office and staff support was provided by CH Charles Perrens.

SYNOPSIS

Addiction, or substance use disorder (SUD), can be characterized by a deregulation of control over the use of reinforcing substances, resulting in persistent use despite negative consequences. Craving, defined as an intense urge to use, is both a diagnostic criterion among the 11 DSM-5 criteria and a fluctuating phenomenon whose daily variations in everyday life explored with the Ecological Momentary Assessment (EMA) have made it possible to propose a validated model of addiction in which cues in daily-life produce craving intensity fluctuations that predict later use, and relapse. This framework giving craving a potential prognostic and etiological value. Craving has been showed as the criterion most frequent and discriminant by Item Responses Theory method but its relationships with other criteria is unknow. Moreover, the presence of craving in subjects with mild addiction suggests that it could be an early marker. On the other hand, while craving is a powerful predictor of use and relapse in the short and medium term (1 year), the long-term impact (5 years and more) of its fluctuations remains unexplored. Consistent with the model of addiction, the cue-reactivity paradigm would lead to both craving and changes in brain and autonomic activity, suggesting that these changes could be the physiological expression of craving. Our hypotheses were that craving is involved in the development and maintenance of SUD, i.e., being a central criterion, in DSM-5 cross-sectional network across all substance users and that the presence of craving is associated with more severity (symptom count) and more use (quantity/frequency). Our hypotheses concerning craving fluctuations were that a better response of craving to treatment at initiation of treatment (i.e.: a more rapid decrease of craving at the beginning of treatment) would be associated with a higher probability for remission at long-term and that craving is associated with a pattern of physiological changes in daily life from cardiac, electrodermal, accelerometer and skin temperature signals.

OBJECTIVES OF THE PhD PROJECT

The main objective was to determine the role of craving in the development of SUD and its severity, its impact on long-term outcomes after initial exposure to treatment and its physiological correlates.

We had 4 *major hypotheses*:

- (1) Craving is involved in the development and maintenance of SUD, i.e., being a central criterion, in DSM-5 network across all substance users;
- (2) The presence of craving is associated with more severity (symptom count) and more use (quantity/frequency).
- (3) A better response of craving to treatment at initiation of treatment (i.e.: a more rapid decrease of craving at the beginning of treatment) is associated with a higher probability for remission at long-term;
- (4) craving is associated with a pattern of physiological changes in daily life from cardiac, electrodermal, accelerometer and skin temperature signals.

To meet our objectives and address our hypothesis we studied craving as a diagnostic criterion (a trait) and a dynamic phenomenon (a state) in two sets (Part I and II) of two studies each (total of 4 studies, considered as 4 individual experiments):

PART I: Explore craving as a diagnostic criterion (trait), first by studying its place and relationship within DSM-5 SUD criteria and by examining its role in the development of SUD.

PART II: Exploring craving as a dynamic phenomenon (state), first by studying the impact of early responses of craving to treatment on long-term outcomes and by investigating its physiological markers in daily life.

PART I: Explore craving as a diagnostic criterion (trait)

Manuscript 1: *“The centrality of craving in network analysis of five substance use disorder”*

Published in Drug and Alcohol Dependence

Background: Among the 11 current diagnostic criteria, craving is a potential central marker for understanding and for treatment of substance use disorder (SUD). Our objective was to explore craving centrality across SUD based on the study of symptom interactions in cross-sectional network analyses of DSM-5 SUD diagnostic criteria. We hypothesized the centrality of “Craving” in SUD across substance types.

Methods: Participants from the ADDICTAQUI clinical cohort with regular use (2 times per week threshold for a substance) and at least one DSM-5 SUD. Outpatient substance use treatment services in Bordeaux, France, were included. Symptom Network Model has been performed on the DSM-5 SUD criteria evaluated over the past 12 months for Alcohol-, Cocaine-, Tobacco-, Opioid- and Cannabis Use disorder.

Results: The sample of 1359 participants, had a mean age of 39 years old and 67% were males. The prevalence of SUD over the time course of the study was: 93% for alcohol, 98% for opioids, 94% for cocaine, 94% for cannabis and 91% tobacco. The only symptom that consistently remained in terms of centrality was “Craving” [3.96 – 6.17] (Z-scores), indicating that it exhibits a high degree of connections in the entire symptom network regardless of the substance.

Perspectives: Identifying craving as central in SUD symptoms network confirms the role of craving as a marker of addiction. This constitutes a major avenue in the understanding of the mechanisms of addiction, with implications to ameliorate diagnostic validity and clarify treatment targets.

Manuscript 2: *“Is craving an early marker of SUD development and severity? A one-year longitudinal follow-up among alcohol and tobacco users not in treatment”*

Submission in progress

Background and aims: Since its inclusion in DSM-5 SUD diagnostic criteria, craving has been shown the most prevalent and discriminant among all criteria in IRT and as a central symptom in network analysis. The aim was to study whether craving could be an early marker of addiction severity by the exploration of its influence on severity of addiction such as DSM-5 diagnostic criteria count, frequency and quantity of use.

Methods: Participants were enrolled in a prospective longitudinal 1-year follow-up study with an assessment of DSM-5 SUD diagnostic criteria, craving and use-related variables every 3 months. First, we differentiated participants according to craving endorsement (always, sometimes and never) to explore the impact of craving on DSM-5 criteria count and the frequency/quantity of use at enrollment and last follow-up. Secondly, to take account of the trajectory over one-year, we used Hierarchical linear modeling (HLM) to explore whether the presence of craving overtime was associated to a greater number of DSM-5 criteria, frequency of use and quantity of use.

Results: 85 participants were included after informed consent. 47.1% (n=40) were female with an average age of 46.3 years (SD=15.2). At enrollment, there was an association between the number of SUD criteria endorsed (excluding craving) and craving endorsement among alcohol ($p<.0001$) and tobacco users ($p<.0001$). At 12-months follow-up, the number criteria endorsed was significantly different between the three groups of craving overtime for participants who used alcohol ($p=.005$) or tobacco ($p=.001$) in sense of gradual increase (Always > Sometimes > Never craving groups). HLM showed that craving at one moment was significantly associated to an increase of criteria number and frequency of use at the same moment for alcohol ($p<.001$; $p=.002$) and tobacco ($p<.001$; $p=.025$) users, but not at the next moment.

Perspectives: Our findings suggest a dose-response association between craving and SUD criteria count, suggesting that the more time goes by, the more craving becomes entrenched, and the more this will lead to the development of other criteria. Craving could be an early marker of addiction severity and its early identification may offer opportunities to intervene before such consequences appear.

PART II: Exploring craving as a dynamic phenomenon (state)

Manuscript 3: “Craving changes in first 14 days of addiction treatment as a predictor of 5 years relapse status”

Submission in progress

Background: Addiction is considered a chronic disorder that requires long-term treatment. Daily fluctuations of craving have been shown to predict substance use and relapse within hours, making it a transdiagnostic target for treatment across substances. Early identification of predictors of long-term outcomes may enable better and early adjustment of treatment. The objective of this study was to examine whether trajectory and temporal dynamics of craving at the beginning of addiction treatment were associated to long-term outcome.

Methods: An Ecological Momentary Assessment study collected craving and substance use during the first 14-days of treatment, followed by prospective regular follow-ups for 5 years or more to assess long-term outcomes. 39 participants beginning addiction treatment for different substances were recruited in an outpatient clinic. Analysis investigated whether individual differences in craving trajectory and dynamics at treatment initiation predicted 5 years or more follow-up outcome: *relapse* versus *remission*.

Results: The results showed that *relapse* status at 5+ years was significantly associated with a slower decrease of craving intensity ($p=.013$), and a lower craving inertia ($p=.038$), during the beginning of treatment, compared to *remission* status. However, craving intensity at the beginning of treatment was not found associated with relapse/remission status at 5+ years follow-up.

Perspectives: Results suggest that a slower decrease in craving at treatment initiation could express a greater resistance to treatment long term. This resistance may have many mechanisms, among which a greater reactivity to cues (as suggested by lower inertia), that could constitute a persistent vulnerability to relapse, and a valuable indicator of long-term outcomes.

Manuscript 4: *“The Autonomic Craving Signature: a pattern of physiological signals associated with craving in daily-life among tobacco, alcohol and cannabis users with SUD”*

Submission in progress

Background: Craving is a strong predictor of use and relapse across different substance use disorders (SUD). Identifying and reporting craving can be difficult for some patients highlighting the need for biomarkers, currently lacking. The aim of this study was to determine a robust methodology for the detection of craving based on physiological measurements captured in daily-life from the combination of ecological momentary assessment (EMA) and wearable sensors among participants with SUDs.

Methods: Individuals with SUD were enrolled in a daily-life study in which craving reported at signal-contingent EMA and at event-contingent by initiation of users, as well as physiological signals [Electrodermal activity (EDA), accelerometer (ACC), skin temperature (TEMP), blood volume pulse (BVP)] were recorded continuously. After labeling “craving” and “no-craving” samples, features of each signal were extracted, normalized, standardized and filtered. Then, a principal component analysis (PCA) was applied. The linear combination of features [Principal Component (PC)] output was used to test several kinds of classifier algorithms.

Results: 43 participants (24 women, 19 men), with a mean age of 32.9 (SD=9.4) years were included for tobacco (n=20, 46.5% of the sample), cannabis (n=14, 32.5%) and alcohol (n=9, 20.9%). EMA completion rate was 85.8% (n=2,017) and in total, 5,512 hours of physiologic data was captured over the course of 14 EMA-days. 384 samples of “craving” (n=192) and “no-craving” (n=192) were analyzed by PCA in which 31 principal components explained 98.8% of variance data. We tested 3 different classification algorithms with which we reached between 58.3% and 73.6% of accuracy.

Perspectives: Performance of our binary classification model was better than a random binary classifier (i.e.: AUC-ROC > 0.55) and this set of features forms a physiological pattern that can distinguish craving from no-craving states and that we labeled *the autonomous craving signature (ACS)*. This is an important breakthrough in the underlying neurobiological mechanisms of craving and paves the way for implications in clinical practice. For clinical practice, the passive detection of craving could be an important step in the development of biomarkers in SUDs.

CONCLUSION

In this PhD project, we confirm the major role of craving as a central criterion in the addiction, and document that it is an early and predictive criterion in the development and severity of addiction. We show that fluctuations in craving intensity at the start of treatment could be a predictive marker of long-term relapse, and that a physiological pattern could distinguish craving from no-craving episodes in daily life.

These results question the relevance of the criteria related to consequences of use, because craving seems to be the only one symptom involved in the development and maintenance of addiction. In daily-life, the study of trajectory of craving at the start of treatment could allow to identify the individual more vulnerable at relapse which could persist overtime and represent early indicators of SUD progression. Moreover, the passive detection of craving would be particularly important, especially in individuals who have difficulty identifying it and leads to hypotheses about the autonomic mechanism involved in SUD and provides a clue as to the underlying functioning of craving.

Thus, this project highlights the role of craving as a driven symptom of addiction and supports its interest as a marker of addiction and pave the way for biomarkers of craving, offering new insights into its underlying mechanisms and new methods of identification and treatment.

Publications and communications directly related to the PhD project:

1 manuscript was published, 3 manuscripts will be submitted soon.

6 oral communications and 5 posters communications in national or international meetings.

LIST OF PUBLICATIONS AND COMMUNICATIONS OF THE PHD STUDENT

Publications and communications directly related to the thesis project

Article published

Gauld* C., **Baillet* E.**, Micoulaud-Franchi J.-A., Kervran C., Serre F., Auriacombe M. The Centrality of Craving in Network Analysis of Five Substance Use Disorders, Drug and Alcohol Dependence 2023: 109828.

**First author*

Article in progress submission

Baillet E., Serre F., Auriacombe A. Making alcohol and tobacco preventable deaths really preventable! Addiction as a modifiable risk factor for alcohol and tobacco preventable mortality. Commentary.

Baillet E., Auriacombe M., Romao C., Garnier H., Gauld C., Vacher C., Fatseas M., Swendsen J., Serre F. Craving changes in first 14 days of addiction treatment as a predictor of 5 years relapse status. Research article.

Baillet E., Serre F., Romao C., Moriceau S., Auriacombe M. Is craving an early marker of SUD development and severity? A one-year longitudinal follow-up among alcohol and tobacco users not in treatment. Research article.

Baillet E., Serre F., Monseigne T., Si-Mohammed H., Jeunet C., Auriacombe M. The Autonomic Craving Signature: a pattern of physiological signals associated with craving in daily-life among tobacco, alcohol and cannabis users with SUD. Research article.

Oral communications

Craving: an early and predictive marker of tobacco, alcohol and cannabis addiction. Scientific day of Doctoral School. 2021, online.

Two-Week Ambulatory Assessment of Craving as a Predictor of 5-Year Addiction Treatment Outcomes. GREPACO, 2021, online.

Le Craving pour le repérage et le traitement des addictions. Intérêt des technologies mobiles en recherche et en clinique : l'addictologie de demain est déjà là ! En co-intervention avec Marc AURIACOMBE, Sarah MORICEAU, Laura LAMBERT, Léa DONNADIEU, Fuschia SERRE. Congrès international ATHS, 2021, Biarritz, France.

Two-Week Ambulatory Assessment of Craving as a Predictor of 5-Year Addiction Treatment Outcomes. L'Albatros/WAAD, 2022, Paris, France.

Advancement of PhD (2021, 2022, 2023). Institut National du Cancer, Paris, France.

The Centrality of Craving in Network Analysis of Five Substance Use Disorders. 2022, College on Drug Dependence Problems, Minneapolis, USA.

Exploration of biomarkers of craving in daily life among tobacco, alcohol and cannabis users. Observational mixed methods pilot study. 2022, Society of Ambulatory Assessment, online.

Posters presentations

Two-Week Ambulatory Assessment of Craving as a Predictor of 5-Year Addiction Treatment Outcomes. **Baillet, E.**, Auriacombe M., Fatseas, M., Swendsen, J., Serre F. Neurocampus Day, 2021, Bordeaux, France.

Exploration of biomarkers of craving in daily life among tobacco, alcohol and cannabis users. Observational mixed methods pilot study. **Baillet, E.**, Romao, C., Moriceau, S., Serre, F., Auriacombe, M., 2022, L'Albatros, Paris, France.

Craving: an early and predictive marker of addiction? Baseline results of a prospective study. **Baillet, E.**, Moriceau, S., Serre, F., Auriacombe, M., 2022, College on Drug Dependence Problems, Minneapolis, USA.

Craving persistence over 3 months: an early and predictive marker of addiction? **Baillet, E.**, Romao, C., Moriceau, S., Serre, F., Auriacombe, M., 2023, College on Drug Dependence Problems, Denver, USA.

Physiological signals in daily life among tobacco, alcohol and cannabis users: Discriminating stress from craving episodes. **Baillet, E.**, Vacher, C., Romao, Bruneau, A., C., Si-Mohammed, H., Jeunet-Kelway, C., Serre, F., Auriacombe, M., 2023, Society of Ambulatory Assessment, Amsterdam, Netherlands.

Publications and communications not directly related to the thesis project

Alexandre, J.-M., Serre, F., Fournet, L., Moriceau, S., Dubernet, J., Sarrazin, S., Bazzani, C., Lambert, L., **Baillet, E.**, Hyves, K., Auriacombe, M., 2021. Le craving, prédicteur de la rechute. *Santé Mentale* : 259, 32-39.

Auriacombe, M., Fournet, L., Dupuy, L., Micoulaud-Franchi, J.-A., de Sevin, E., Moriceau, S., **Baillet, E.**, Alexandre J.-M., Serre, F., Philip P., 2021. Effectiveness and Acceptance of a Smartphone-Based Virtual Agent Screening for Alcohol and Tobacco Problems and Associated Risk Factors During COVID-19 Pandemic in the General Population. *Frontiers in Psychiatry*: 12.

Serre F., Gauld C., Lambert L., **Baillet E.**, Micoulaud-Franchi J.-A., Auriacombe M. Dynamic Networks to explore predictors of substance use among patients beginning treatment for substance use disorder. *Submission in progress*.

Prizes and awards

- NIDA Travel Award to CPDD meeting, Minneapolis, USA (2022)
- Poster Award in meeting of Addiction(s) et Territoires en Nouvelle-Aquitaine, Poitiers, France (2022)
- Poster Award in meeting of Addiction(s) et Territoires en Nouvelle-Aquitaine, Limoges, France (2023)

Tasks performed and skills acquired during my PhD

Project management

- **ECEDA study.** One-year longitudinal prospective study to explore the evolution of DSM-5 SUD diagnostic criteria among general population. This study is funded by my doctoral PhD grant by French Institute of Health (Institut National du Cancer & Institut de Recherche en Santé Publique – INCa-IReSP_15746) following a call for doctoral grant applications: "Fighting against psychoactive substance use and addictions" ([RESULT OF AAP SPADOC](#)). In collaboration with appropriate staff, *I managed the regulatory process for approval of protocol according to French Regulation for research with Human Subjects (Personal Protection Committee, CNIL, authorization RCB 2021-A01220-41) and was responsible for its implementation in my host lab.*
- **BIOEMA study.** Cross-sectional observational study in daily life lasting 14 days using the EMA (Ecological Momentary Assessment) method and wearable sensor. This study is funded by my doctoral PhD grant by French Institute of Health (Institut National du Cancer & Institut de Recherche en Santé Publique – INCa-IReSP_15746) following a call for doctoral grant applications: "Fighting against psychoactive substance use and addictions" ([RESULT OF AAP SPADOC](#)). In collaboration with appropriate staff, *I managed the regulatory process for approval of protocol according to French Regulation for research with Human Subjects (Personal Protection Committee, CNIL, authorization CPP EST III, 2021-A01835-36) and was responsible for its implementation in my host lab.*

Teachings

- **University of Bordeaux – Master degree (1 & 2) of International Neurosciences Program – 46 hours**
 - UE addiction of Pr. M. AURIACOMBE – Master 2 (30 hours)
 - Biomarkers of addiction
 - Neurobiology of addiction
 - Methods for the study of addictive behavior in human
 - Human model in addiction
 - UE Démarche expérimentale du Pr. M. DARNAUDERY – Master 1 (10 hours)
 - Follow-up group of students working on articles by Neurocampus researchers
 - Internship report defense jury for students – Master 1 (6 hours)
- **University of Bordeaux – Bachelor degree (2 & 3) of Sciences & Technology Program – 32 hours**
 - UE Professional Opening – Licence 2 (24 hours)
 - UE Professional Opening – Licence 3 (8 hours)
- **University PSL (Paris Sciences & Lettres) – Ecole Pratique des Hautes Etudes (EPHE) – 2 hours**
 - Non-degenerative diseases: human model of addiction (2 hours)

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- Communicating in a foreign language (25h): English conversation workshops;
- Develop your interpersonal skills: Vulgarisation Scientifique - Bureau des Enquêtes (Cap Sciences) ;
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- Clinical assessment tools: Addiction Severity Index (ASI), Mini International Neuropsychiatric Interview (MINI), Ecological Momentary Assessment (EMA);
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ABBREVIATIONS LIST

ACC: Accelerometer	EEG: Electroencephalography
ADDICTAQUI: Addiction Aquitaine Cohort	EDA: Electrodermal Activity
ANS: Autonomic nervous system	EMA: Ecological Momentary Assessment
APA: American Psychiatry Association	ESM: experience sampling method
aPFC: Anterior prefrontal cortex	FFT: Fast Fourier Transform
AR: Autocorrelation	fMRI: functional magnetic resonance imaging
ASQ: Associated Situations Questionnaire	FN: False negative
ASI: Addiction Severity Index	FP: False positive
AUC: Area under the curve	HAIS: Hanil Alcohol Insight Scale
BIOEMA: Biological and Ecological Momentary Assessment	HLM: Hierarchical Linear and non-linear Modeling
BVP: Blood Volume Pulse	HR: Heart Rate
CAGE: Cut Down, Annoyed, Guilty, Eye-opener	HRV: Heart Rate Variability
CDS: Cigarette Dependence Scale	ICC: Intraclass correlation
CSAPA: Centre de Soins, d'Accompagnement et de Prévention en addictologie	ICD: International Classification of Disease
CPP : Comité de Protection des Personnes	IPL: Inferior parietal lobule
DA: Dopamine	IRT: Item Responses Theory
dACC: Dorsal anterior cingulate	LDA: Linear Discriminant Analysis
dfPFC: Dorsolateral prefrontal cortex	MDM: Minimum distance to mean
dmPFC: Dorsomedial PFC	MSSD: Mean square successive difference
DSM: Diagnostic and Statistical Manual of Mental Disorders	MINI: Mini International Neuropsychiatric Interview
ECA: Embodied Conversational Agent	MoCA: Montreal Cognitive Assessment
ECEDA: Explore Craving for Early Detection of Addiction	NAc/Vs: Nucleus accumbens/ventral striatum
ECG: Electrocardiogram	NCS: Neurobiological Craving Signature
	OCDS: Obsessive-Compulsive Drinking Scale

OFC: *Orbitofrontal cortex*
PA: *physical activity*
PCA: *principal analysis component*
PDA: *personal digital assistant*
PET: *Positron emission tomography*
PNS: *Parasympathetic nervous system*
PPG: *Photoplethysmography*
PTN: *Perception of treatment need*
rMSSD: *Root mean square of successive differences*
ROC: *receiver operating characteristic*
sgACC/rACC: *Subgenual/rostral anterior cingulate*
SCR: *Skin conductance responses*
SD: *Standard deviation*
SNS: *Sympathetic nervous system*
SUD: *Substance Use Disorder*
SVM: *Support vector machines*
TEMP: *Skin temperature*
TN: *True negative*
TP: *True positive*
vlPFC: *Ventrolateral prefrontal cortex*
WHO: *World Health Organization*

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INTRODUCTION

PART I: Addiction & Craving

1. Historical perspective of addiction and craving

The word “*addiction*” finds its roots in the of latin term “*ad-dicere*” that signifies “bound to” or “enslaved by”. During the first Roman Republic period, this term was used in legal domain to refer to someone who was unable to pay his debts and therefore became the slave of its creditor, until their debts were fully repaid (Rosenthal and Faris 2019). In this term, we find two essential notions of this disease: constraint and loss of freedom. This term continued to evolve outside of its strictly medical use and has been used to describe habits or passions of people in different domains: the person is described as “addicted to”. The use of the term “addiction” happened much later, when the development of psychiatry allowed to characterize addiction as a disease of the mind (Rosenthal and Faris 2019).

Indeed, for thousands of years, there have been reports of abnormal consumption of a substance or behavior which refers to addictions (Brousse and de Chazeron 2014). In Antiquity, the key element on which this disease is based is said to be “*a driving force that pushes one to consume despite the negative consequences*” (Aristote). Even back then, there were many references to loss of control in addictions, and specifically to craving, this intense desire to use (Brousse and de Chazeron 2014, Auriacombe, Serre et al. 2018b): in the 18th century, Lettsom refers to the loss of control of “*drunkards*” and that “*their alcohol has become as necessary as food... Neither threats nor convictions are powerful enough to overcome [for alcohol craving], and the unhappy victim deprived of procuring the fatal object is so infatuated, as in spite of so many locks and key, to bribe the nurse on whom he depends for the success of his scheme...*” (Lettsom 1787). Then, Kerr refers to craving by the description of “pathological deprivation of the appetite center” and the urge to drink alcohol as “Tantalus’ punishment whose thirst cannot be quenched” (Kerr 1888). The notion of imperiousness in addictions, which can refer to craving, was already raising many questions: first associated with opiate-related withdrawal (Wikler 1948), then distinguished in 1955 with the differentiation by the World Health Organization (WHO) of “no-symbolic craving” corresponding to physical withdrawal and “symbolic craving” associated to a loss of control and relapse (Jellinek, Isbell et al. 1955). But the concept of craving is controversial, with some

suggesting that it is an epiphenomenon that cannot explain relapse, or that it is simply a habit of consumption. A definition of craving emerged in the 1990s, based on its compulsive and obsessive nature (Modell, Glaser et al. 1992, Pickens and Johanson 1992, Tignol 1992), then in the 2000s with advances in neuroimaging and addiction treatments targeting loss of control (Anton 1999, Drummond, Litten et al. 2000). Today, craving is a major and pivotal concept in addiction, that we explored in more detail in this PhD.

2. Is Addiction, a disease like any other? Stigma of people who use addictive substances

Addiction is a health problem associated with an important social stigma, including among health professionals (Cazalis, Lambert et al. 2023) . Although there is no consensus about the definition of stigma, it can be considered as “a marker of shame, disgrace, or disapproval which results in an individual being rejected, discriminated against, and excluded from society” (Dannatt, Ransing et al. 2021). There is a greater stigma surrounding substance addiction in comparison to mental illnesses (Lloyd 2013) since addiction is not socially considered as a mental disorder, but also because the use of substances classified as “illegal” calls for a moral judgment. This stigmatization is a fundamental barrier to the improvement of addiction treatment and this is why it is important to understand what led people to harshly judge addiction, in order to overcome this stigma. From a functionalist point of view, humans are driven to construct some meaningful explanations for their condition, to understand why and how they are sick (Taussig 1980). A disease can be explained by the individual's actions, lifestyle, and relation to the natural and social environments. With the 18th century and their progress in discovery of organisms responsible of many diseases, functionalist explications became less extensive except for cases where biological causes don't apply, such mental diseases, including addiction. Assessment of neurobiological damage has been abandoned as a basis for diagnosis and diagnosis is based solely on functional investigations of individual behavior. This approach can contribute to self-stigma because the person with addiction is perceived as the cause of the disease. This perspective remains anchored in our society where some people stay convinced that people with addiction are responsible of their disease by a lack of motivation. This stigma is internalized by people that use substances and it will lead to reduced self-esteem, self-efficacy and trust in the future (Henderson and Dressler 2017) that

may furthermore reduce their individual capacity for making decisions including access to health care. Scientific research is “a potent weapon against stigma, one that forces skeptics to let go of misconceptions and stereotypes” (Services, (U.S.) et al. 1999). Also, it seems essential to reduce stigma among both researchers and clinicians, starting with our ways of writing and speaking that reveal how we make these people exist in the world. This is why in this manuscript, people who use addictive substances and people who meet criteria for addiction will be described as such and not as addict, or addicted person or user (Hartwell, Naberhaus et al. 2020, Traxler, Nicks et al. 2021). This is our contribution to reduce addiction-related stigma (Atkins, Dopp et al. 2020).

3. What is addiction? The concept of the *disease of use*

The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) defines substance use disorders (SUD) as a constellation of behaviors involved in compulsive drug seeking including impaired control of substance use, impaired social interactions with others because of substance use, risky drug use (e.g., substance use in hazardous settings), and pharmacological changes (e.g., experiencing withdrawal symptoms and tolerance). Addiction is characterized by a substantial loss of self-control, displayed in compulsive drug-seeking behavior despite the desire to discontinue use (American Psychiatric Association 2013, Volkow, Koob et al. 2016). Addiction can be defined in many different ways, but one definition adopted in the medical field is that addiction is a chronic, relapsing disorder, characterized by a compulsion to seek and take substances and the loss of control to regulate substance intake. Addiction may be defined as a dysregulation of control over use of rewarding substances and behaviors that translates into repeated and excessive use despite the experience of negative consequences (Auriacombe, Serre et al. 2018b). Excessive use expresses loss of control that is considered the core of SUDs. It is important to distinguish the fundamental or core symptoms of a phenomenon from ancillary or consequential symptoms to understanding the intern construct of that phenomenon. If the loss of control concept is considered as core to addiction, it must be differentiated from the surrounding constellation of preexisting risk factors and consequences whether toxicological, physical or environmental (Auriacombe, Serre et al. 2018). Addiction represents a relapsing and chronic disorder and unfortunately has many public health consequences.

4. What is the health impact of addiction? The invisible causality of “preventable” deaths.

Addiction is among the most prevalent and deadly form of psychopathology (Steel, Marnane et al. 2014). Because of the carcinogenic and toxic properties of many addictive substances, any use presents a health risk and is associated with health issues such as hepatitis C, HIV/AIDS, risks of cancer, cardiovascular, digestive or nervous system diseases, brain damages, and many traumatic consequences, particularly through road accidents (Zibbell, Asher et al. 2018, Al-Zalabani 2020). Tobacco and alcohol are reported as being the first lead of so-called preventable deaths (Degenhardt, Charlson et al. 2018, World Health Organization 2021). Worldwide, tobacco and alcohol kill respectively more than 8 and 3 millions people each year (World Health Organization 2018, World Health Organization 2021). Other substances such as cocaine (Haas, Karila et al. 2009), cannabis (Degenhardt, Whiteford et al. 2013) or opiates should not be overlooked as they are equally dangerous and deadly. Opioids (including heroin, morphine, codeine, fentanyl, methadone, tramadol...) represent a worrying case, especially in the United States. The initial legitimate concern to facilitate access to opioid analgesia in the late 80's with new products such as oxycodone (called 'OxyContin') or hydrocodone (called 'Vicodin') may have been overpromoted by some pharmaceutical companies and underassessed for their side-effects by health authorities (Robert, Jouanjus et al. 2023). Today, it is a real epidemic in the USA: in 2017, approximately 2 million Americans were estimated to have opioid use disorder, and the number of fatal overdoses involving opioids reached 47,600 (Florence, Luo et al. 2021). Worldwide, about 0.5 million deaths attributable to drug use (UNODC 2021) and with heroin overdoses quadrupling in 5 years initially began by using prescription painkillers (Koh 2015). However, we need to keep in mind that, worldwide, access to opiate analgesics remains insufficient (Berterame, Erthal et al. 2016).

All users of addictive substances will not develop addiction (Swendsen and Le Moal 2011), but some regular users of such substances may already have a SUD (Marel, Sunderland et al. 2019) especially those that use in highly larger quantities which make them more at risk of consequences and complications including death. The prevention of complications will be contingent to the prior detection of SUD, that affects 4% of the general population excluding alcohol and tobacco (Grant, Saha et al. 2016) and 15-20% of the general population when

including these substances (Hughes, Helzer et al. 2006). Because users are considered as voluntarily exposing themselves to alcohol and tobacco, these substances are the focus of campaigns that promote cessation or reduction of use such as “Stoptober” (encourages smokers to abstain from smoking during the months of October) or “Dry January” (encourages drinkers to abstain from drinking during the months of January) (Kuipers, West et al. 2019, de Ternay, Leblanc et al. 2022). Such deaths are considered “preventable” but it is not really the case if the user meets criteria for addiction, which is the case for many that use high quantities that expose them to more toxic consequences and a higher need for prevention. **A commentary of this point was carried out during the thesis and is available in the Appendix 1.**

A better understanding the mechanisms involved in SUD will allow researchers to develop treatment interventions and prevention strategies that are more efficient to reduce millions of current deaths from substance use disorder. **This research is dedicated to the people who have lost their lives to addiction.**

5. Risk factors of SUDs: the gene-environment interaction

Many risk factors for SUD development are related to complex interactions between *biological factors* (genetics, epigenetics, developmental), *environmental factors* (familial environment, trauma, social and cultural systems), psychological trait (novelty, sensation seeking, reactivity to stress), and the *substances* (Swendsen and Le Moal 2011, Merikangas and McClair 2012, American Psychiatric Association 2013, Volkow and Boyle 2018, Ahmed, Badiani et al. 2020).

The **genetic factors** play a role in vulnerability or protection against SUD and could contribute to approximately 50% of risk for addiction (Volkow and Li 2005). The genes identified as being involved in this risk, influence biological responses to substance use (Yu and McClellan 2016). Some genes encoding for the nicotinic receptor have been found to be highly associated with vulnerability to nicotine addiction (Etter, Hoda et al. 2009). About **epigenetic factors**, the National Institutes of Health describes it as “*refer[ring] to both heritable changes in gene activity and expression (in the progeny of cells or of individuals) and also stable, long-term alterations in the transcriptional potential of a cell that are not*

necessarily heritable” (Kantor 2008). Epigenetic mechanisms contribute to SUD phenotype: it has been shown that exposure to addictive substances induces epigenetic modifications directly associated to addiction-related behavioral abnormalities (Nestler 2014). **Developmental factors** are also risk factors as the adolescent brain is characterized by a stage of important changes in growth and connectivity, the exposure to addictive substance at this development stage may increase adolescent’s vulnerability to the effect of substances and may impact brain development (Giedd 2008). The early-adolescent onset of substance use (UD) is as marker of risk for later development of SUDs (King and Chassin 2007). The contribution of biological factors as ovarian hormones should be given more consideration in SUD research. Furthermore, a growing body of research has associated **gut microbiome composition** to the vulnerability to addiction (for reviews: (Qin, Hu et al. 2021)). For example, researchers showed that the gut microbiota, that refers to intestinal bacteria, influenced brain functions (neuroinflammatory responses such as mood and behavior, myelin synthesis...) and could be a new target for SUD treatments (Leclercq, Stärkel et al. 2019).

Environmental factors influence the vulnerability to develop SUD. Low average socioeconomic status, younger age, limited income and other sociodemographic variables could be associated with use (Anthony, Warner et al. 1997, Hasin, Stinson et al. 2007), but this would depend on the type of substance (for reviews: (Karriker-Jaffe 2011)). These aspects may interact such as genetic and environmental aspects: gene-environment interaction (Pasman, Verweij et al. 2020). Genetic vulnerability combined with adverse environmental circumstances will promote deleterious outcomes, while conversely, a beneficial environment may protect against the effect of genetic vulnerability (Shanahan and Hofer 2005). For example, individual vulnerabilities (preexisting mental illness, chronic pain...) combined with promotive environment (access to substances ...) influence substance use experimentation risk and later prevalence of SUD (Volkow, Michaelides et al. 2019).

Individual’s **psychological trait** also influence the risk and prevalence of SUD such as impulsivity, novelty and sensation seeking and stress reactivity (Franques, Auriacombe et al. 2003, Jasinska, Stein et al. 2014, Holmes, Hollinshead et al. 2016). Few studies have examined the **role of sex** on different aspects of SUD. However, the few available studies in animal models have shown differences in the development of addiction-like characteristics, such as

compulsive substance use, increased motivation for the substance, increased need for the substance, and vulnerability to relapse, where female animals develop more readily than male animals (Lynch and Taylor 2004, Perry, Westenbroek et al. 2015, Kawa and Robinson 2019, Towers, Bakhti-Suroosh et al. 2021). This effect called “telescoping effect” refers to course of development and/or seeking treatment for SUD that are more readily in women than in men (for reviews: (Towers, Williams et al. 2023)).

Substances play a role in vulnerability to develop SUD. Substances have different pharmacological properties and toxicological actions on brain substrates. The risk of addiction varies by the intrinsic addictive properties of substances that are linked with different activation levels of the reward system and route of administration (oral, nasal, smoke, intravenous) (Strang, Bearn et al. 1998).

6. What role does pleasure play in addiction? Role of reinforcement and conditioning processes

6.1 Pleasure to ensure survival

One of the main aim of brain is to maintain a balance of internal environment: homeostasis is the concept by which an organism can maintain internal stability while adjusting to changing external conditions by self-regulated process (Billman 2020). The role of homeostasis is to ensure our survival by having the body act to restore imbalances as they are created. Pleasure is the motivation for physiology-oriented behaviors. It was used by evolution to encourage us to eat, drink, find a partner to reproduce, protect against cold (Cabanac 2013). Thus, pleasure is a sign of usefulness and displeasure a warning sign. Seeking of pleasure and avoidance of displeasure leads to homeostatic behaviors. Sensory pleasure therefore indicates a useful stimulus and simultaneously motivates the subject to use it. Both a reward and a motivation, pleasure leads to optimization of life. Pleasure acts as a reinforcement that produces a sequence of motivated behaviors terminated by consummatory behavior usually elicited by the reinforcer. It is a key element in the body's natural rewards. There are a many different types of reinforcers: natural reinforcers, social reinforcers but also external object like psychoactive substances or behaviors that have fundamentally reinforcing properties

(substance pharmacological effect for example) and which will acquire additional reinforcing properties through reinforcement processes.

6.2 The reinforcement processes

Reinforcement processes play a role in the pathways to addiction. The experiences of one individual with the effect of the substance will have an important impact on that individual's future consumption. Substances that interact with the brain have reinforcing properties that can be either positive or negative. In the first case, **positive reinforcement**, there is an *addition* of something that will increase a *behavior*: one person will have an experience with a substance effect (*addition*) and this will lead to repeat substance use (*behavior*). Indeed, positive reinforcement is the process by which presentation of a stimulus, such as a substance, increases the likelihood of a response like substance taking. That means that if experiencing substance taking is pleasurable, this feeling will positively reinforce substance use, making the person more likely to take the substance again. In the case of **negative reinforcement**, there is a removal of something that will increase a behavior: one person will alleviate negative feelings (*remove*) with a substance effect and this will lead to substance use again (*behavior*). The negative reinforcement is the process by which removal of a stimulus such as negative feelings or emotions, increases the likelihood of a response like substance taking. Indeed, substance use is then driven by negative feelings such as anxiety, depression or stress. The relief of negative feelings through substance use results in negative reinforcement, which increase the likelihood that the person will use again. All substances used in the case of positive or negative reinforcement increase the likelihood of using again. Reinforcement is underpinned by a learning process called conditioning.

6.3 Conditioning processes

Substance use may involve two types of learning that can be combined and will increase the likelihood of using again: classical and operant conditioning. **Classical Conditioning** is one in which the organism learns something through association of a neutral stimulus with a biologically significant stimulus to produce a conditioned response. In the context of addiction, classical conditioning occurs when neutral stimuli (such as places, people, or objects) become associated with substance use, which is the biologically significant stimulus. Over time, these neutral stimuli acquire the power to elicit a conditioned response,

such as craving, or wanting or the desire to use, simply by being present (Tiffany 1990). **Operant Conditioning** is the type of learning in which the organism learns by way of modification in behavior or pattern through reinforcement or punishment. It is a learning process based on the consequences of behavior. When a behavior is followed by a reward or positive reinforcement, it tends to be strengthened, meaning its frequency increases. In the context of addiction, substance use can be reinforced by the pleasurable or euphoric effects it produces. Thus, the individual is more likely to continue using that substance to obtain these rewards, which reinforces the “substance-seeking” behavior. Additionally, operant conditioning can also involve negative reinforcement, where drug use is used to eliminate or avoid unpleasant feelings or withdrawal symptoms.

7. Addiction Treatment and care

Treatment for SUD is a process of modifying use behavior to achieve the most stable remission of the disease, by maintaining abstinence or a significant reduction of use. The central goal is to anticipate and avoid relapse (so called relapse prevention). Relapse is a complex phenomenon (Witkiewitz and Marlatt 2007) and the natural evolution of SUD due to the impairment in the control of use of addictive substances. Relapse refers to a return to a previous level of substance use after a period of considerable reduction or abstinence from substance use (Witkiewitz and Marlatt 2007, Moe, Moltu et al. 2022). When assessed on change in relapse frequency, treatment of SUD is very effective but will require long-term treatment acceptance, as it is for other chronic diseases (O'Brien 2008). The aim is to act on the relapse phenomenon by reducing its frequency and intensity when it occurs. The primary base of treatment for SUD is the identification of a high-risk situation that could increase risk for a person to engage in using. Coping strategies are developed to help the person with addiction to deal with these high-risk situations. To date, craving appears among the best documented risk factor for relapse (Vafaie and Kober 2022) and consequently a major target for treatment (Auriacombe, Serre et al. 2018b). Despite the fact that SUDs have comparable treatment efficacy to other chronic conditions (van den Brink 2012), it is estimated that less than 15% of people that meet criteria for an addiction receive treatment (treatment gap) (Gerada 2005) and a majority of the general population and health professionals not specialized in addiction still believe addiction treatment is not useful (Avery, Avery et al. 2020).

8. What basis to diagnoses addiction? Nosographic classifications.

Nosography allows to describe and organize diseases. Diagnostic systems are essential to communicate both between researchers, clinicians and patients; and to have a basis for precision in research. In the field of mental health and addictive disorders, there are mainly two classifications for illnesses: the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM).

8.1 Diagnosis of addiction according to ICD

The ICD system, which is under the auspices of the WHO, published the eleventh revision of ICD (ICD-11) in 2016 (International Classification of Diseases-11 2016), some 25 years after the tenth revision (ICD-10). ICD designed the addictive disorder as “the Substance Use and Related Disorders”. Currently, substance addiction and dependence is “a disorder of regulation of substance use arising from repeated or continuous use of it” (World Health Organization 2017). The current ICD classification subdivides psychostimulants into cocaine on the one hand, and other stimulants such as amphetamine-type compounds and caffeine on the other. Gambling disorder is included in the Substance Use and Related Disorders chapter in the ICD-11. To make a diagnosis of Substance dependence, an individual must exhibit two or more of the three main characteristics (**Table 1**) simultaneously and repeatedly for a minimum of 12 months or continuously for at least one month.

Table 1 from (International Classification of Diseases-11 2016). Diagnostic criteria for substance dependence from ICD-11

	<i>Diagnostic criteria</i>	<i>Criteria definition in ICD-11</i>
1	Impaired control	Impaired control over substance use – in terms of the onset, level, circumstances of termination of use, and often, but not necessarily, accompanied by a subjective sensation of urge or craving to use the substance
2	Substance use becomes increasing priority	Substance use becomes an increasing priority in life such that its use takes precedence over other interests or enjoyments, daily activities, responsibilities, or health or

		personal care. It takes an increasingly central role in the person's life and relegates other areas of life to the periphery. Substance use often continues despite the occurrence of problems.
3	Physiological features	Physiological features (indicative of neuroadaptation to substances) as manifested by: (i) tolerance, (ii) withdrawal symptoms following cessation or reduction in use of substance, or (iii) repeated use of substance to prevent or alleviate withdrawal symptoms. Withdrawal symptoms must be characteristic for the withdrawal syndrome for substance and must not simply reflect an effect of excess use.

8.2 Diagnosis of addiction according to DSM

The last version of the DSM (DSM-5), published by the American Psychiatric Association, was published in 2013, nearly 20 years from the time of publication of the fourth edition (DSM-IV). In DSM-5, the addictive disorders are named substance use disorders (SUDs) in the "Substance-Related and Addictive Disorders" section and it represents a combination of diagnostic features of DSM-IV substance dependence and substance abuse. The diagnostic term of "SUD" refers to recurrent use of reinforcing substances or behaviors causing clinically and functionally significant impairment, such as health problems, social/professional disrupting, or difficulties to meet its responsibilities. The DSM-5 lists ten separate types of substance addictions: alcohol; caffeine; cannabis; hallucinogens; inhalants; opioids; sedatives, hypnotics or anxiolytics; stimulants; and tobacco. There are several modifications since the DSM-IV version. First, the "gambling disorder" (previously called "pathological gambling") is a new entity of DSM-5 while the "internet gaming disorder" was included in "conditions for further study" chapter of DSM-5. Secondly, by addition/omission of some criteria: the "craving" criterion was added and the "legal problems" criteria was omitted from the DSM-5 diagnosis.

Also, since 2013, SUD based on DSM-5 is defined as "a problematic pattern of substance use leading to clinically significant impairment or distress" and is characterized by a set of 11-diagnostic criteria, which we will detail in **Table 2**. The diagnosis of SUD is defined by presence

at least 2 criteria among all criteria in the 12-months period. Disease severity is based on criteria count: endorsement of two to three criteria is categorized as having mild SUD, four to five as moderate, and six to 11 criteria as severe.

Table 2 from (American Psychiatric Association 2013). DSM-5 SUD diagnostic criteria.

	<i>Diagnostic criteria</i>	<i>Criteria definition in DSM-5</i>
1	Large amount/longer	<i>"Using greater amounts of the drug than intended"</i>
2	Quit/control	<i>"failing to quit or control drug use despite the desire to do so"</i>
3	Time spent	<i>"spending substantial time on drug-related activities"</i>
4	Craving	<i>"Craving or urge, strong desire or urge to use"</i>
5	Neglect role	<i>"failing to fulfill major responsibilities at work, school, or home"</i>
6	Social/interpersonal problem	<i>"continuing drug use despite social problems"</i>
7	Activities given up	<i>"giving up other activities because of drug use"</i>
8	Hazardous use	<i>"using drugs in physically risky situations"</i>
9	Psychological/physical problem	<i>"Continuing drug use despite physical or psychological problems"</i>
10	Tolerance	<i>"showing signs of tolerance (need for increasing amount to achieve intoxication)"</i>
11	Withdrawal	<i>"showing signs of withdrawal"</i>

9. Make the difference: loss-of-control and consequences of loss-of-control

In DSM-5, SUD is characterized by 11 diagnostic criteria (American Psychiatric Association 2013) and conceptually, these criteria (or symptoms) can be grouped into subcategories of impaired control over substance use (Symptoms 1 – 4), social impairment (5 – 7), risky use (8 – 9), and physical dependence (10–11) (**Table 3**) (American Psychiatric Association 2013, Suzuki and Kober 2018). The first 4 criteria are considered as the expression of loss of control,

whereas the following criteria are considered consequential and grouped by area of consequence. Indeed, the first group (loss of control) describes the core of addiction while the next three groups are considered peripheral, as they are the consequences of the loss of control (Martin, Langenbucher et al. 2014, Auriacombe, Serre et al. 2018b). It is important to distinguish peripheral features from "core" or "central" features of the disorder. Core features can be defined as symptoms and constructs that directly reveal the underlying internal dysfunction of the disorder, such as loss of control over use. Peripheral features do not directly index these internal dysfunctions (loss of control), but its consequences. The consequences of the disorders (loss of control over use) have long been used to characterize and diagnose use disorders due to the absence of etiology (American Psychiatric Association 2013). Over the past decades, many researchers have focused on a particular symptom of loss of control: craving.

Table 3 adapted from DSM (American Psychiatric Association 2013) and from (Auriacombe, Serre et al. 2018). Distinguish between the core of addiction and its consequences.

		<i>Subcategories</i>	<i>Diagnostic criteria</i>	<i>Definition in DSM-5</i>
CORE	1	Loss of control	Large amount/longer	<i>"Using greater amounts of the drug than intended"</i>
	2		Quit/control	<i>"Failing to quit or control drug use despite the desire to do so"</i>
	3		Time spent	<i>"Spending substantial time on drug-related activities"</i>
	4		Craving	<i>"Craving or urge, strong desire or urge to use"</i>
PERIPHERAL	5	social impairment	Neglect role	<i>"Failing to fulfill major responsibilities at work, school, or home"</i>
	6		Social/interpersonal problem	<i>"Continuing drug use despite social problems"</i>
	7		Activities given up	<i>"Giving up other activities because of drug use"</i>

	8	Risky use	Hazardous use	<i>"Using drugs in physically risky situations"</i>
	9		Psychological/physical problem	<i>"Continuing drug use despite physical or psychological problems"</i>
	10	Pharmacologic adaptation	Tolerance	<i>"Showing signs of tolerance (need for increasing amount to achieve intoxication)"</i>
	11		Withdrawal	<i>"Showing signs of withdrawal"</i>

10. Craving, a core symptom of addiction. What is it?

10.1. Craving, a dimensional phenomenon with predictive validity in addiction

Craving is defined as an unwanted, intense and persistent desire or urge to use (Auriacombe, Serre et al. 2018b). It is described as an intrusive and egodystonic experience in which thoughts and behaviors are in conflict or dissonance with the needs and goals of the individual. Craving is an "abnormal desire" that is distinct from normal desire and characterized by longing, yearning and physiological need for a substance (Tiffany and Wray 2012). Craving has re-emerged as a relevant concept in the context of its inclusion in the DSM-5 revision of the SUD diagnostic criteria in 2013 (American Psychiatric Association 2013, Hasin, O'Brien et al. 2013). **It can be studied as a diagnostic criterion, meaning a trait that is present or absent; and as a fluctuating phenomenon meaning a state that vary in intensity over time.**

Indeed, craving is an internal experience that fluctuates overtime both in intensity and frequency. Craving occurrence and intensity can vary rapidly over the course of a day: the same individual (i.e., *intraindividual variations*) may experience several episodes of cravings during the same day, but with different durations and intensities (Sayette, Shiffman et al. 2000). People frequently describe strong fluctuations in craving with peaks (Drummond, Litten et al. 2000, Tiffany, Warthen et al. 2009) which translates their brevity. Moreover, these characteristics of craving fluctuations differed greatly from one person to the next due to important *interindividual variations*. The cessation of use has an effect by causing an increase in the intensity and frequency of craving from the first day of stopping (McCarthy, Piasecki et

al. 2006) then a decrease over a short period (2-weeks) in patients with treatment (Shiffman, Engberg et al. 1997). However, overtime, craving can persist people may experience cravings even years after quitting. Treatment initiation, pharmacologic or not, contribute to decrease the craving in the first weeks of cessation (Shiyko, Lanza et al. 2012) but other factors can influenced craving fluctuations.

10.2. Craving is influenced by the environment

These fluctuations of craving in frequency, intensity or duration can be influenced by different factors: internal (i.e., emotions), external (i.e., context) or interindividual (i.e., psychopathology) (Epstein, Willner-Reid et al. 2009). Among factors the most important that increase craving, there is the context (i.e., places, other users, the moment of day, social pression, conflict...), the presence of addictive substances, the availability or ban of substances, emotions (negative or positive), stress, tiredness ... The effect of these different factors would be all the stronger in the case of cues. Cues are conditional stimuli that have been associated with past experiences of drug use or addictive behaviors, and that can trigger a conditioned response such as craving, regardless of the presence of the addictive substance or object behavior (Tiffany 1990, Childress, Hole et al. 1993, Carter and Tiffany 1999). Cues can be classified into two main categories: exteroceptive (external) and interoceptive (internal) (Robbins and Everitt 1999). External cues come from the external environment, such as visual, auditory, tactile or olfactory signals (i.e., smell of cigarette smoke, ashtray...), while internal cues come from the body's internal environment, such as physical or emotional sensations (i.e., feel stressed) that may come from the activation of the insula, a brain region involved in the perception of these sensations (Naqvi and Bechara 2009). They can activate these two separate pathways, exteroception and interoception, and lead to the craving response (Betts, Dowd et al. 2021). The craving response can be triggered by a single type of cue or by a combination of exteroceptive and interoceptive cues.

Inversely, there are factors that decrease craving as trait characteristics of individuals and/or their environment (McKay, Franklin et al. 2006), levels of motivation and self-efficacy (Hopkins, Spears et al. 2022), meaningfulness (Knapp, Brick et al. 2021), or pharmacological treatments targeting craving (Serre, Fatseas et al. 2015). Other factors can influence craving variations such as psychiatric comorbidity (Weinstock, Alessi et al. 2007, Calabria, Degenhardt

et al. 2010), alexithymia (Saladin, Santa Ana et al. 2012), novelty seeking (Zilberman, Tavares et al. 2007), impulsivity, trait inhibition (Papachristou, Nederkoorn et al. 2012) or SUD severity (Tiet, Ilgen et al. 2007).

10.3. How to measure/capture craving?

Craving, by its fluctuating characteristic which can be influenced by several factors, makes its measurement difficult: not all assessment methods are equal to study quick fluctuations and peaks of craving, influence of cues and link with use (Cavicchioli, Vassena et al. 2020, Reichert, Gan et al. 2021). If all tools or methods are not equal to assess this phenomenon, different factors can explain it: (1) reliability of self-assessment measure of craving (e.g.: validity of scale, items...); (2) condition of craving assessment (e.g.: assessment in real-life, lab or clinical setting, experimental paradigms...) or craving induction (e.g.: paradigm of cue-reactivity, negative affect exposure...); (3) temporality between craving and another phenomenon (e.g.: prospective, momentary or retrospective assessment). **Thus, craving can be measured in 2 ways.**

10.3.1 Measure craving as trait (diagnostic criterion)

The recent development of well-validated measures of craving (Sayette, Shiffman et al. 2000, Tiffany, Carter et al. 2000) in different samples (Rosenberg 2009) allows to access craving by different ways: single-item ratings (visual analogic scale or numeric scale) or multi-item questionnaires. We can count a least 24 tools to measure craving (Cavicchioli, Vassena et al. 2020). **The main common of these tools is that craving is measured by its absence or its presence especially being diagnostic criterion in DSM-5.** It is measured as a trait which occurs within a given temporality of the tool (e.g., in the last 30 days by Addiction Severity Index or in the past 12-months by DSM-5) or which does not occur. Indeed, the temporality of craving assessments differs also from one tool to another: “retrospective” assessment refers to anterior period or “momentary” assessment refers to at this moment. Retrospective measures have the disadvantage of memory bias, such as lumping of episodes, or on the contrary, selecting some episodes and not others.

10.3.2 Measure craving as a state (fluctuating phenomenon)

To overcome this limitation of retrospective memory and take account the fluctuating characteristics of craving, the use of technology, such as smartphone, is very useful especially in contexts closer to real-life conditions. With the help of mobile technology, the use of daily life monitoring, such as Ecological Momentary Assessment (EMA) (Stone and Shiffman 1994), allows real time measurements of individual momentary states such as craving, **allow its study as a dynamic phenomenon by fluctuation of intensity overtime.**

It has 3 main advantages:

- **Ecological validity:** use in the natural environment to observe behaviors (i.e., use) and feelings (i.e., craving) in the contexts in which they occur;
- **Realtime collection:** allows to limit memory bias (Stone and Shiffman 1994)
- **Repeated measurements:** to examine intra-personal fluctuations in individual experiences (such as craving) and to approach causality by examining the timing of events via prospective analyses. They can be useful in understanding not only the intensity, but also the duration and peaks of craving (Sayette, Martin et al. 2005).

The EMA has been adapted to the study of craving and shown to be feasible and valid in individuals with addiction to various substances at treatment initiation (Serre, Fatseas et al. 2012).

PART II: Craving as a trait: what is its role in addiction? Could it be an (early) marker of addiction?

In this part, craving has been studied as a trait, i.e., it was considered as a diagnostic criterion characterized by its presence or absence.

1. How much is craving special as a diagnostic criterion? Psychometric approach.

Item Responses Theory (IRT) is a latent variable method to assess dimensional and structural validity of diagnostic criteria (Embretson and Reise 2000). This method enables the exploration of underlying latent constructs and the psychometric properties of items, considering diseases as disorders, which are underlying phenomena causing symptoms. In IRT, directly observed clinical symptoms are explained in terms of latent constructs, meaning that symptoms are attributed to the underlying disorder. IRT analyses assess the psychometrics of criteria by exploring the difficulty of the criterion to be endorsed, corresponding on a value of the latent trait severity, and the discrimination from subjects that do not have the disorder. The main objective of IRT is to model the relationships between item responses and the underlying traits. This information, applied to SUD, provides an underlying latent construct with criteria distributed along the severity continuum and has been studied in the context of SUD for several substances (Hasin, O'Brien et al. 2013, Shmulewitz, Greene et al. 2015, Serier, Venner et al. 2019). IRT analyses applied to DSM-5 SUD criteria showed that the newly introduced craving fit well with the other criteria on the SUD underlying unidimensional latent variable and its addition did not change the psychometric properties for other criteria (Hasin, O'Brien et al. 2013, Serier, Venner et al. 2019). These analyses showed that craving was the least difficult to endorse, i.e. the most prevalent/frequent, and the most discriminant, i.e. its presence or absence was able to better differentiate sick from non-sick, among all DSM-5 diagnostic criteria when comparing substances (Kervran, Shmulewitz et al. 2020) (**Figure 1**), when adapted to food (Chapron, Kervran et al. 2023) and between regular users samples (Shmulewitz, Keyes et al. 2011, Chung, Martin et al. 2012, Gilder, Gizer et al. 2014, Castaldelli-Maia, Martins et al. 2018, Kervran, Shmulewitz et al. 2021, Shmulewitz, Stohl et al. 2021). Craving is a special diagnostic criterion because it seems the most selective criterion among

all DSM-5 SUD diagnostic criteria. The high discriminating power of the craving criterion suggests that it is the most informative criterion for the latent trait that corresponds to the underlying factor (Chung, Martin et al. 2012, Kervran, Shmulewitz et al. 2020). This IRT method involves considering psychiatric illnesses, here addiction, as being the product of a single underlying cause, the “latent variable” (Borsboom, Fried et al. 2017) and does not provide information about interrelationships between each criterion and how the presence of one criterion may influence the other ones.

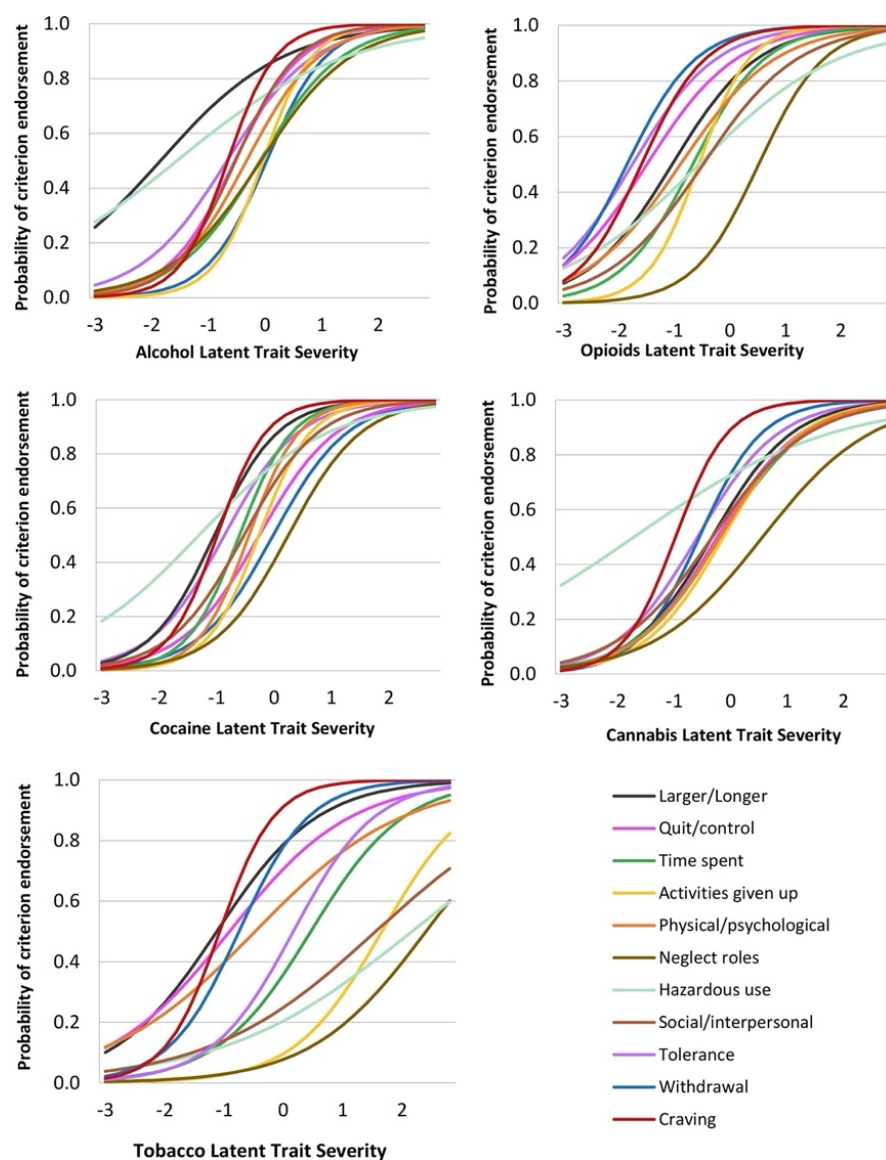


Figure 1. from (Kervran, Shmulewitz et al. 2020). Probability of criterion endorsement across the severity continuum from IRT models of alcohol, opioids, cocaine, cannabis and tobacco DSM-5 use disorder.

2. Craving is a central potential criterion in SUD network? Networks approach.

Recent research proposes to conceptualize psychopathological behaviors as a network where each symptom is considered as an interacting component (Borsboom and Cramer 2013). In network theory, symptoms are dynamically directly related to each other and consist of nodes representing observed variables connected by edges representing statistical relationships (Epskamp, Rhemtulla et al. 2017). Instead of interpreting symptoms as a function of a set of underlying/latent disorders, the network approach conceptualizes symptoms as elements of a complex network that are causally mutually dependent and often mutually reinforcing (Cramer, Waldorp et al. 2010, Borsboom and Cramer 2013). Each symptom of a disease is considered to have a causally and active part in the network. This kind of model is used in a large and diverse number of disorders (Fried 2015, McNally, Heeren et al. 2017) such as depression or anxiety (Beard, Millner et al. 2016), social anxiety (Heeren, Jones et al. 2018), post-traumatic disorder (McNally, Robinaugh et al. 2014) or other types of disorders such as pathological grief (Robinaugh, LeBlanc et al. 2014) or sleep disorders (Gauld, Lopez et al. 2021). The inferences offered by such networks allow to approach causality of disorder and to better understanding of how disorders develop, are maintained and could be treated (Borsboom and Cramer 2013, Borsboom, Fried et al. 2017).

The network framework is an appropriate conceptual approach in the context of SUD where symptoms may be in interaction, such as many other mental disorders. For example, drinking more alcohol than expected is often the first symptom of an alcohol use disorder (Buu, Wang et al. 2012), consistent with the fact that loss of control over drinking is a strong predictor of problem drinking (Leeman, Patock-Peckham et al. 2012). This network theory has been conceptualized in the context of SUD, for the DSM-III-TR (Rhemtulla, Fried et al. 2016) that showed that “Large amount” criterion (*“Using greater amounts of the drug than intended”* – Table 2) is the most central from all criteria in a sample of adults (Rhemtulla, Fried et al. 2016) and adolescents (Buu, Wang et al. 2012). However, craving was not present in DSM-III-TR and it could not be included in these analyses. Recent network analysis on comparison of DSM-IV and DSM-5 SUD diagnostic criteria showed that “Time spent” criterion was the most central across all criteria (Rutten, Broekman et al. 2021) (**Figure 2**). Although all other criteria were included as a standard diagnostic criterion (i.e., assessed over the past 12-

months), analysis did not include craving as diagnostic criterion but only as an estimate by dichotomizing the score of the abridged 5-items version of the self-administered Obsessive-Compulsive Drinking Scale (OCDS) where craving was evaluated only over the past 7-days and thus exposing to the risk of underestimating the potential role of craving in the network. **To date no study of SUD with all diagnostic criteria directly explored over the past 12 months have explored their network characteristics.**

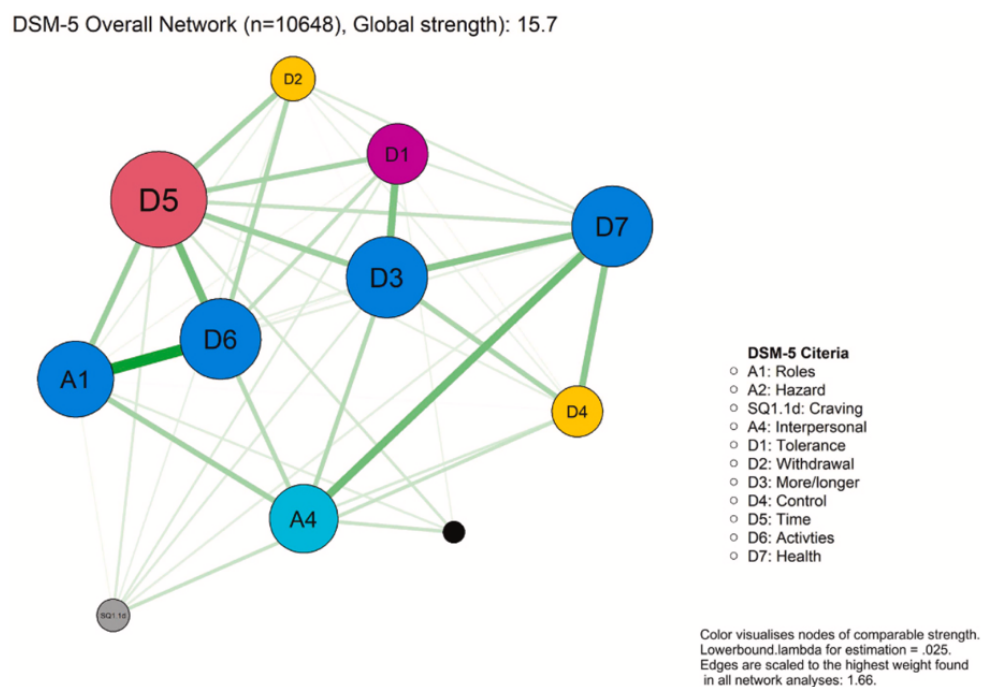


Figure 2 from (Rutten, Broekman et al. 2021). Overall DSM-5 symptoms network from SUD patients in treatment for alcohol, cannabis, cocaine, stimulants and opioids.

3. Craving: is it the first symptom to appear in SUD development?

In DSM-5 SUD, craving is a diagnostic criterion included among core symptoms. It is one of the most central processes in SUDs because it leads to relapse and is already a treatment target (Sayette 2016, Serre, Fatseas et al. 2018, Auriacombe, Serre et al. 2018b, Cavicchioli, Movalli et al. 2020). Moreover, as seen previously, craving is the most frequent and discriminant among all DSM-5 SUD diagnostic criteria indicating that it is present at all stages of the severity continuum and that it allows to distinguish sick from non-sick users (Kervran, Shmulewitz et al. 2020). Craving was the most endorsed criterion among 11 DSM-5 criteria with others criteria of loss of control (use longer than planned, failing to quit or control use

despite the desire to do so) in cannabis problematic users and these same criteria were endorsed in majority in all SUD severity levels (60% in mild, 70% in moderate and 90% in severe groups) (Fink, Shmulewitz et al. 2022). Craving in subjects with even mild SUD suggests that it may be among the first symptoms to appear or may be in itself an expression of the disorder (Chung, Martin et al. 2012), suggesting the importance of studying it dynamically over time in the SUD. Researches with IRT and network methods, used cross-sectional data, it means collected variables such as SUD criteria, at a single point in time (Wang and Cheng 2020). These studies do not provide information on track changes over time, compared to longitudinal studies. In one longitudinal study conducted among school student sample, assessments of loss-of-control criteria includes craving in early stages of alcohol use suggest that the early onset of craving or difficulty controlling use may be prognostic indicators of future risky drinking and potential alcohol problems (Morgenstern, DiFranza et al. 2016). Research in tobacco use has shown that craving can appear within days to weeks of the onset of occasional use, and could constitute the first self-reported symptoms of SUD (DiFranza, Rigotti et al. 2000, Gervais, O'Loughlin et al. 2006). Thus, cross-sectional and longitudinal studies suggest that craving could be the most informative criterion about SUD and could be the first symptom to appear. Results are fundamental because loss-of-control symptoms and especially craving could be part of SUD core and potentially constitute etiologic symptoms of the disease. It would be an invaluable tool for prevention, both for early detection and to avoid the development of greater severity. However, these longitudinal studies were conducted only in adolescents that presents unique characteristics which must be in considerations (Grant, Levine et al. 2005, Grant, Williams et al. 2007) and results about this sample could be not representative of SUD in adult sample. To overcome limitations of these studies, it would be important to set-up a longitudinal study among adult sample to understanding whether some criteria, such craving, could be predictive of SUD development or more highly severity levels development. **To date no study has explored, in longitudinal data with a sample of adults, whether craving could be an early symptom of SUD.**

4. Hypotheses

It would be fundamental to examine the relationship between DSM-5 SUD diagnostic criteria and to approach the causality of SUD among substance users using cross-sectional network analysis. **We supposed that craving is involved in the development and**

maintenance of SUD, i.e., being a central criterion, in DSM-5 network across all substance users.

Furthermore, exploring the role of craving in a longitudinal study would provide a better understanding of the development of TLUS, especially among substance adult users not in treatment or not requesting access to treatment. **We supposed that the presence of craving is associated with more severity (symptom count) and more use (quantity/frequency).**

PART III: Craving as a state. Is it a marker of long-term use outcome? What are its biomarkers?

In this part, craving has been studied **as a state**, i.e., it was considered as a fluctuating phenomenon whose intensity and frequency vary over time.

1. A human model of addiction: cues – craving – use

This EMA method allowed to validate the theoretical and generic model of addiction, cues – craving – use model proposed by Sanpsy Lab and validated both for substances and behaviors (Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2015, Auriacombe, Serre et al. 2018b) (**Figure 3**).



Figure 3 from (Auriacombe, Serre et al. 2018b). Cues – craving – use, human model of addiction.

In this model, there is a prospective link between cues, craving and use where:

- Increasing of number of cues in the environment was associated with increasing of craving intensity self-reported on the next EMA survey, with a more important increase of craving induced by individual-specific cues compared to standardized generic cues (Fatseas, Serre et al. 2015);
- Increased intensity of craving at one moment is associated with increased likelihood of using primary substance on the next EMA survey, this link craving – use being unidirectional, craving predicts use and not the other way (Fatseas, Serre et al. 2015).

This link craving – use has been confirmed in several EMA studies (Serre, Fatseas et al. 2015, Panlilio, Stull et al. 2019, Cavicchioli, Vassena et al. 2020, Burgess-Hull, Panlilio et al. 2022, Ellis, Mun et al. 2022).

2. Trajectory of craving and measures of its dynamic

2.1 Craving Dynamic Measures: variability, instability and inertia

Beyond measuring intensity at any given time and its influence on the next-moment that does not account for the influence of time, recent literature in psychology and psychiatry has shown the importance to take into account the dynamic variability of symptoms over time. Dynamic metrics are used to analyze the dynamics of a variable and understand how it evolves over time: they allow to characterize fluctuations, changes and temporal dependencies in the data. Three dynamics metrics able to characterized moment-to-moment changes and that have been frequently examined: variability, inertia (or temporal dependency) and instability (Trull, Solhan et al. 2008, Trull, Lane et al. 2015).

2.1.1 *The variability*

The **variability** reflects the deviation in momentary affect from the individual's average affect level that is most often calculated by the within-person standard deviation (SD) (Houben, Van Den Noortgate et al. 2015, Trull, Lane et al. 2015). Variability entails the extremity of affect levels that a person experiences and refers to the degree of dispersion or differences in values within a variable overtime. It characterizes the changing nature of the phenomena being studied. High variability indicates that the values of the variable fluctuate considerably, reflecting significant changes in that variable over time. In contrast, low variability suggests that the levels of the variable are relatively stable, with less pronounced fluctuations. To illustrate, the left two panels of **Figure 4** display possible patterns of emotional change characterized by low (showing less deviations from the mean) versus high (showing larger deviations from the mean) variability based on simulated data (Schoevers, van Borkulo et al. 2021).

2.1.2 *The inertia*

The **inertia** is the temporal dependency components of affective dynamics. Greater temporal dependence of affect reflects a tendency for affect to be highly predictable from moment to moment and so reflect change in response to fluctuating environmental demands (Kashdan and Rottenberg 2010). A high inertia reflects a tendency to persist from one moment to the other, and can reflect lower sensitivity in response to fluctuation in environmental

demands. Conversely, low inertia indicates low time dependence, meaning that current values are less influenced by past values. Affective inertia refers to the within-person autocorrelation (AR1) of affect assessed repeatedly over time (Kuppens, Allen et al. 2010). It is the correlation between craving at time t and affect at time $t-1$ for each individual and, in a second step, correlating these within-person autocorrelations with between-person measures of well-being or psychopathology. To conclude, inertia refers to within-person autocorrelation between consecutive measures (Trull, Lane et al. 2015). High inertia indicates high time dependence, meaning that current values are strongly influenced by previous moment. To illustrate, the bottom right panels of **Figure 4** show simulated data patterns characterized by low versus high inertia.

2.1.3 *The instability*

The **instability** can be defined as the magnitude of symptom changes from one moment to the next (Lamers, Swendsen et al. 2018) and is conceptualized as the combination of variability and inertia (or temporal dependency) (Ebner-Priemer, Kuo et al. 2007) (**Figure 4**). While variability (i.e., the within-person SD) reflects the overall amplitude of affective changes (i.e., how much affect deviates around its mean level), inertia (i.e., the within-person autocorrelation) reflects the consistency of the moment-to-moment affect between adjacent measures. The instability can be measured using a single index that considers both these two components: the mean square successive difference (MSSD) (Jahng, Wood et al. 2008) which is the average squared difference between each pair of subsequent observations within a single participant. It reflects the extent to which consecutively measured symptoms differ from one another and thus incorporates both the magnitude of symptoms changes and their temporal order. Instability can be calculated by the root mean square of successive differences (rMSSD) which expresses instability on the original affect item scale and is also corrected for positively skewed MSSD scores (Jahng, Wood et al. 2008). High instability indicates high variation or volatility in the values of the variable, while low instability indicates relative stability of values. To illustrate, the top panels of **Figure 4** show simulated data patterns characterized by low versus high instability.

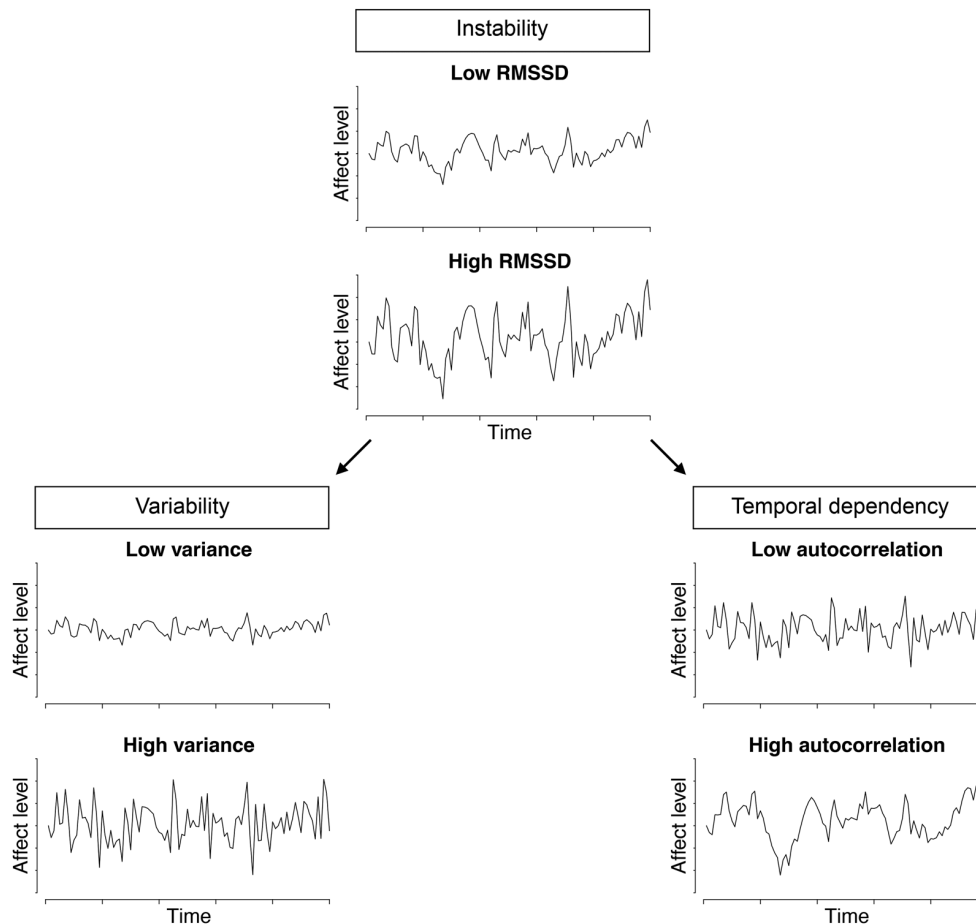


Figure 4 from (Schoevers, van Borkulo et al. 2021). Illustration of the 3 components of affect fluctuations patterns: instability, variability and inertia.

Top panel: Instability measures the fluctuation or rapid changes in a variable over time.

Bottom left panel: Variability measures fluctuations and differences in the values of a variable over time. *Bottom right panel:* Temporal dependency or inertia allows us to understand how the values of a variable evolve and are related to their history or to the environment.

2.2 The use of dynamic measures in psychiatry field

In psychiatry field, it is particularly adapted to study emotional fluctuations because these patterns can reflect how people deal with changes in the environment and how they regulate their emotions (Larsen 2000). These metrics have been used in EMA studies to capture dynamic processes of mood disorders (Lamers, Swendsen et al. 2018, Johns, Di et al. 2019, Panaite, Rottenberg et al. 2020), obsessive-compulsive disorders (Landmann, Cludius et al. 2019), and more recently, substance use disorders (Chirokoff, Abdallah et al. 2022, Ellis,

Mun et al. 2022). For example, a meta-analysis revealed a greater emotional inertia in individuals with depressive and anxiety symptoms (Houben, Van Den Noortgate et al. 2015) and several studies showed a greater mood instability observed in individuals with major depression, bipolar disorder and anxiety disorders (Jones, Hare et al. 2005, Ebner-Priemer, Kuo et al. 2007, Pfaltz, Michael et al. 2010, Thompson, Mata et al. 2012). The greater instability in negative affect at the treatment initiation was linked with low response to treatment in depressed patients (Wichers, Peeters et al. 2010, Husen, Rafaeli et al. 2016).

In addiction field, most work on dynamic measures has focused on smoking or heavy drinking. For example, studies in adolescents show that mood variability at baseline differentiated escalation of smoking over time during one year from those who never progressed, and that among adolescents who escalated their smoking, mood variability levels was more stable followed this increase (Weinstein, Mermelstein et al. 2008). Also, affect fluctuations were more important during days of alcohol use (Jahng, Solhan et al. 2011) and affect and stress fluctuations were stabilized after alcohol use (Dvorak, Stevenson et al. 2018). Affect fluctuations seems to be able to predict substance use where emotion fluctuation was associated with higher frequency of alcohol, tobacco and cannabis user from those with emotion regulation. Other studies extending this work of fluctuation to other populations, such as treatment-seeking populations. Indeed, some researchers used these dynamic measures to explored craving in addiction. Recent study found that individuals with higher craving variability had lower risk of relapse compared to individuals with lower craving variability (Cleveland, Knapp et al. 2021). The examination of intra-individual variability indices in outpatients being treated with MOUD (Medication for Opioid Use Disorder) shown that a greater magnitude of craving variability was significantly associated with opioid use (Ellis, Mun et al. 2022). It seems that the study of fluctuations in craving or affect at the beginning of treatment, and thus of the early response to treatment, provides information on short-term relapse.

3. Relapse at short- and long-term

Relapse is a major phenomenon in the treatment of SUDs since 85% of patients relapse and reuse the addictive substance within a year of starting treatment (Brandon, Vidrine et al. 2007) and on average, people achieve stable abstinence (one year or more) only after 3 to 4

treatment episodes over several years (Dennis, Scott et al. 2005). Many factors can influence and precipitate relapse, including both so-called “distal” and “proximal” factors (Witkiewitz and Marlatt 2004). Distal factors include characteristics of individuals and/or their environment (McKay, Franklin et al. 2006), levels of motivation and self-efficacy (Hopkins, Spears et al. 2022), meaningfulness (Knapp, Brick et al. 2021), psychiatric comorbidities (Weinstock, Alessi et al. 2007, Calabria, Degenhardt et al. 2010), or SUD severity (Tiet, Ilgen et al. 2007). These distal factors could make the individual more vulnerable to relapse, or to more proximal triggers such as craving (Moore, Seavey et al. 2014, Serre, Fatseas et al. 2018) or stress (Sinha 2001). Craving is currently considered by many authors a major treatment target to reduce relapse frequency (O'Brien 2005 a, Auriacombe, Serre et al. 2018, Vafaie and Kober 2022). The link craving – use has been confirmed in several EMA studies that reported a positive association between an increase in craving at a given time, and an increase in the likelihood of reporting substance use within minutes (O'Connell, Shiffman et al. 2011), hours (Berkman, Falk et al. 2011, Fatseas, Serre et al. 2015, Panlilio, Stull et al. 2019, Cleveland, Knapp et al. 2021, Ellis, Mun et al. 2022) or days (Piper, Federmen et al. 2008, Cofta-Woerpel, McClure et al. 2011). A few studies report a positive association between craving and relapse in the following weeks (Piper, Federmen et al. 2008, Bolt, Piper et al. 2012, Shiyko, Lanza et al. 2012, Burgess-Hull, Panlilio et al. 2022). The beginning of SUDs treatment seems be important to outcomes because craving intensity during the first week of smoking cessation has also been shown to be associated with abstinence at the end of treatment, and over the course of 6 months following treatment (Piper, Federmen et al. 2008). Interestingly, one study observed a faster decrease of tobacco craving at the beginning of treatment in individuals who remained abstinent within the first month, compared to those who relapsed (Shiyko, Lanza et al. 2012). A recent metanalysis including both EMA and non-EMA studies concluded on a strong prospective relationship of self-reported craving with future substance use / relapse, even for medium term intervals (over 1 year) (Vafaie and Kober 2022). Thus, the set of studies confirming that craving is an important proximal trigger for relapse in daily-life but for longer intervals (5 years or more), results of EMA studies remained mixed (Serre, Fatseas et al. 2015). Furthermore, dynamic metrics can shed light on the dynamic nature of craving and its course overtime and could be a precious information for the influence of its trajectory overtime on use/relapse. A recent study shown subtypes in craving trajectory at treatment initiation that producing differences in short-term outcome such as use: high and increasing craving Group

had the highest rate of use during treatment than everyone groups (Burgess-Hull, Panlilio et al. 2022). Thus, early craving changes at treatment initiation appear to be informative about short-term treatment responses. **However, it remains to be explored whether these changes of craving at treatment initiation may represent a potential predictor of longer-term outcomes.** Indeed, identifying early indicators of disorder progression would enable to adjust treatment intensity and duration accordingly, to better prevent relapse and increase treatment effectiveness, as for many other chronic diseases (Konerman, Yapali et al. 2014, Lai, Dimko et al. 2015, Greenberg, Jacobson et al. 2022).

4. The lack of insight ability in SUD

4.1 A major problem to access in treatment

Many people who need substance use treatment do not perceive need for treatment (Lipari, Park-Lee et al. 2013). This could also be explained by the absence of perception of treatment need (PTN) (Goldstein, Craig et al. 2009, Moeller and Goldstein 2014) that is a major component of clinical insight (David, Bedford et al. 2012), regulated by neural circuits underlying interoception and self-awareness (Goldstein, Craig et al. 2009, Moeller and Goldstein 2014). In other terms, it is the inability for some to understand their disease severity and the need to take care of. This inability is called insight deficit (or interoception deficit) and is defined, although not unanimously (Jaafari and Marková 2011), as the inability for some people with SUD to be aware of their own condition and to seek help (Dandaba, Ebrahimighavam et al. 2020). This term is used to refer to the perception and awareness of individuals of their disorders and their ability to perceive and construct a correct representation of their illness (Lysaker and Bell 1994, De Sousa, Romo et al. 2012). This ability seems to be essential to take account of its symptoms and disease, to realize the need of care and to initiate treatment of SUD. Indeed, impaired clinical insight and poor perception of the need for treatment contribute to a lack of willingness and/or attempt to stop using and would be the main explanation for not seeking treatment (Probst, Manthey et al. 2015). Among individuals with SUD, around 78% had low PTN (Moeller, Platt et al. 2020) and for instance, the most severe smokers, i.e. those using more, were those that are never trying to stop using and were more likely to deny consequences of tobacco use (could be interpreted as low clinical insight) (Jarvis, Wardle et al. 2003). Moreover, this is consistent with the fact that

people in care often have higher levels of clinical insight than the general population (Raftery, Kelly et al. 2020). Beyond to less initiation of treatment and reduced treatment outcomes response (Lambert, Serre et al. 2022), clinical insight has impact to realizing and reporting craving.

4.2 Reporting craving: an ability available to all?

Individuals with poorer clinical insight tend to underestimate or even deny the existence of their symptoms (Rinn, Desai et al. 2002) including craving. Indeed, it could be related to dysfunction of interoceptive system regulated by the insula: the association between activity of the insula and craving intensity being greater among individuals with good abilities of interoception, i.e. a greater ability of consciousness of internal states (Antons, Brand et al. 2020). The difficulty to report craving could be due to a deficit in systems of self-awareness and of insight regulated by the insula and the anterior cingulate cortex (Goldstein, Craig et al. 2009, Moeller and Goldstein 2014). Recently, a study showed that participants with low PTN, which means low insight, retrospectively reported less frequent craving, compared to participants with good insight for the same SUD severity (Lambert, Serre et al. 2021). This dysfunction of the interoceptive system, that leads to underestimation of craving, could lead to difficulties in the context of care to identify the risk of relapse and the impact of treatment; and in the context of research to identify craving and its association with use/relapse (Cavicchioli, Vassena et al. 2020). **It would be important to be able to measure craving regardless of the individuals' self-report ability and so to study the possibility of developing biomarkers of craving in SUD.**

5. Cue-induced paradigms: physiological responses to cues or physiological expression of craving?

Many studies in lab settings have also shown that cues lead to increasing craving intensity since decades (Childress, Hole et al. 1993, Carter and Tiffany 1999) and it could be mediated by conditioning or learned association (Niaura, Rohsenow et al. 1988). In addition to craving, other responses can be collected depending of the measures used in the cue-reactivity paradigm. The cues-exposure paradigm involves exposing drug-related cues (e.g.: images of people engaging in drug use, smell, touch...) and neutral stimuli (e.g.: household objects) and

comparing the responses evoked by them. The cue-reactivity are responses to exposure drug- and non-drug related-cues and may be (1) **brain responses** measured by brain imaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET) or electroencephalography (EEG); (2) **physiological variations**, include those controlled by the autonomic nervous system (ANS), measured by physiological monitors such as Electrodermal Activity monitors (EDA), electrocardiogram (ECG), or photoplethysmography (PPG); or (3) **mental phenomenon** as like craving collected by self-reported scale. Cue-reactivity paradigm led to both brain-responses, physiological responses, underpinned by changes in ANS which may be expressed by a higher physiological arousal as well as higher self-reported craving.

5.1 Brain-responses associated with craving by cue-induced paradigm

Several studies from a meta-analysis (Chase, Eickhoff et al. 2011), identified a significant correlation between (1) the amygdala and craving magnitude (Murphy, Lubman et al. 2018) and (2) ACC and craving (Kühn and Gallinat 2011). The first correlation was not found in another meta-analysis (Kühn and Gallinat 2011) but this could be due to methodological issues, especially with regard to experimental design which can influence the lateralization of amygdala, left amygdala being more involved in block designs for example (Murphy, Lubman et al. 2018). Moreover, some studies showed no correlation between higher activation of cortical and subcortical regions and craving scores, however, craving was correlated with less deactivation of some regions (Wang, Zhornitsky et al. 2021). A correlation between an increase of DA release in dorsal striatum and an increase of craving magnitude was showed by PET study (Volkow, Wang et al. 2006). Dopaminergic dysfunction in the striatum may attribute incentive salience to substance-associated stimuli, so that cues elicit craving and excessive activation of neural networks associated with attention and behavior control (Heinz, Siessmeier et al. 2004). This set of studies suggest that craving could be underpinned by automatic network which could be identify. Recently, one study published in Nature Neurosciences examined the neuromarker of craving i.e. fMRI markers that predicts the intensity of drug and food craving and able to distinguish drugs users from non-users (Koban, Wager et al. 2023). From cue-exposure paradigm and fMRI, authors used machine learning to identify a functional brain activity pattern that predicted intensity of craving. This important study suggests that (1) food and drug craving are similar and have shared neurobiological

mechanisms; (2) craving may be identified physiologically by a pattern called “neurobiological craving signature” (NCS) and (3) this NCS was able to discriminate substance users (with SUD and/or heavy users) from non-users without SUD based on NCS response to substance and food cues (Koban, Wager et al. 2023). The NCS includes the vmPFC and cingulate cortices, VS/NAc, temporal/parietal association areas, mediodorsal thalamus and cerebellum (Koban, Wager et al. 2023) (**Figure 5**). After these fundamental findings on the first fMRI-based neuromarkers of drug and food craving, it would be important to identify other correlates of craving such as psychophysiological responses to cues.

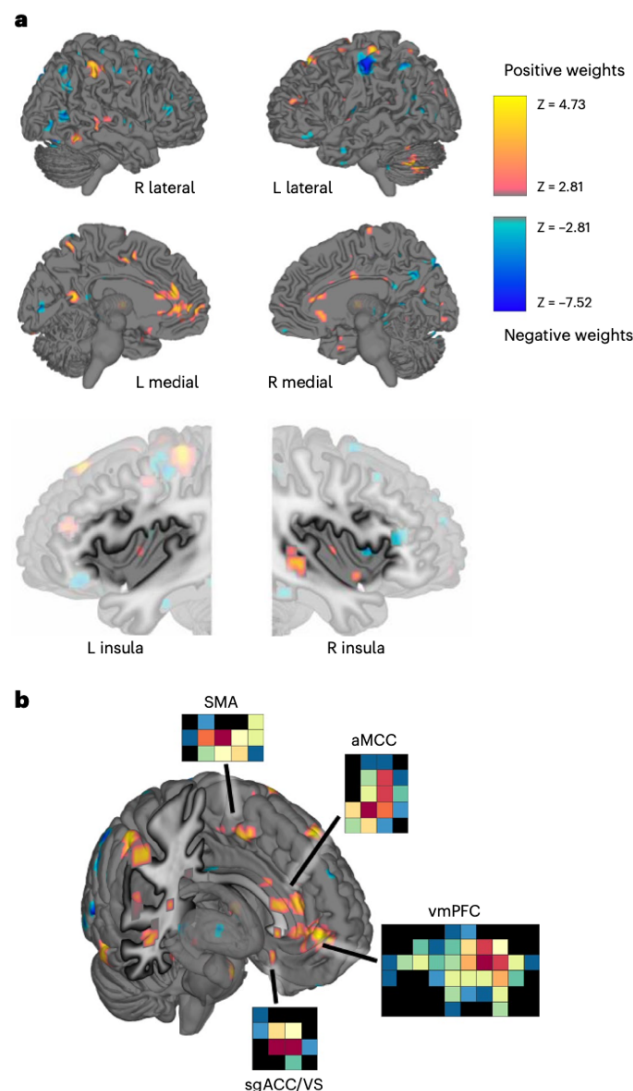


Figure 5 from (Koban, Wager et al. 2023). The brain areas most involved (negatively or positively) in the predictive pattern of craving, i.e., the NCS.

5.2 Physiological-responses associated with craving by cue-induced paradigm

Several studies examined craving and psychophysiological responses to cues at the same time. In study by Kaplan and collaborators (1985), the self-report of craving and the increase of skin conductance level (SCL) was positively correlated and this only among individuals with alcohol addiction (Kaplan, Cooney et al. 1985) and in the same sense, the study showed a positive correlation between alcohol cue-elicited craving and skin conductance response (SCR) among men drinking alcohol but not meeting criteria for addiction but not in women (Wang, Zhornitsky et al. 2019). Individuals using alcohol showed an increase in heart rate (HR) and salivary cortisol and at the same time an increase in craving during the cue-exposure paradigm (Sinha, Fox et al. 2009), as did individuals using heroin, who showed an increase in physiological arousal (SC, muscle electromyography, skin temperature, HR, blood pressure, diastolic blood pressure) and craving (Zhao, Fan et al. 2012). In smokers, cortisol secretion was correlated with magnitude of craving in daily smokers but not occasional smokers in response to stressors (Buchmann, Laucht et al. 2010). Individuals smoking tobacco exposed to cues experienced changes both in physiological responds and in self-reports of craving (Drobes and Tiffany 1997), and this was also found for individuals drinking alcohol, smoking tobacco (Drobes 2002) or using cocaine (Childress, Ehrman et al. 1988). Indeed, several literature reviews suggests cue-reactivity paradigm can elicit increases in self-report of craving and significant physiological reactions in different kinds of addictions. In the case for alcohol, tobacco, heroin, cocaine addictions when individuals with addiction are exposed to substance-related stimuli (Niaura, Rohsenow et al. 1988, Rohsenow, Niaura et al. 1990). Across all substances (tobacco, alcohol, heroin, cocaine), HR increases when exposed to substance-related stimuli, as well as electrodermal activity, in comparison to neutral stimuli. Skin temperature (TEMP) increases under the same conditions, but the results were inconsistent for alcohol and tobacco (Carter and Tiffany 1999). At the same time, craving was increased under these conditions of cue-exposure. Although there are significant effects for both, effect could be greater in self-report of craving compared to physiological effects (Carter and Tiffany 1999). Three primary physiological measures that could be perceived as indicators of craving include HR, EDA, and TEMP (Carter and Tiffany 1999).

5.3 Limits of cue-induced craving paradigm

Indeed, this set of studies showed that there is a cooccurrence between the appearance of physiological or neurofunctional variations and the appearance/increase in craving. **These brain and physiological manifestations may be the physiological expression of craving.** Physiological responses can be used to an indirect measure of craving, for several reasons. To begin with, the awareness of craving might independently trigger psychophysiological arousal; or, stimuli that have been previously linked to drug withdrawal or drug consumption could evoke both subjective craving and psychophysiological arousal simultaneously. This conceptualization is consistent with the incentive sensitization theory of addiction in which the interaction between associative learning and neuroadaptations in the brain that occur due to repeated drug use. Indeed, conditioning process increase the incentive value of these cues, leading powerful secondary reinforcers that can capture attention and elicit craving (Tiffany and Wray 2012). Stimuli with incentive salience can elicit craving for unconditioned rewards as well as craving for the stimuli themselves. Third, psychophysiological responses might act as conditioned stimuli that trigger craving. Fourthly, the individual that use a substance may interpret self-awareness of changes in physiological arousal as subjective craving. And finally, physiological responses could be physiological expression of craving. Such craving can be unconscious (physiological) or conscious (craving). However, some results are inconsistent and studies are mixed (Tong, Bovbjerg et al. 2007) and could be explain by the used paradigm.

Indeed, there are two reasons for which cue-exposure paradigm could not be an appropriate method to study craving and its physiological responses. Firstly, it is known that craving may appear without any cues, naturally. Craving is an intrusive phenomenon that could be automatic and that can occur naturally, without being provoked by anything or anything conscious. In this instance, measuring craving and its physiological responses only after exposure to cues may not be appropriate, as it does not generalize to all craving. Secondly, cue-exposure paradigm (such as other paradigms) to measure craving or physiological responses, entails mechanisms that are not limited to addictive disorders but instead share similarities with the convergence of information pathways involved in processing reward, emotional responses, non-declarative memory, and obsessive-compulsive behavior (Noori, Cosa Linan et al. 2016). Indeed, all these studies suggest that craving could have physiological change associated with its appearance. Cue-exposure studies have typically

been conducted in laboratory setting that is a controlled environment. This is an advantage to control variables and induce craving or others responses. Yet, it seems that physiological responses and craving could be affected by the environment (negative or positive affect, substance availability, social interaction, place...) and this may not represent the individual's true reactions to his natural environment (Shiffman, Li et al. 2015). **Thus, it would be very important for a better understanding of craving, regardless of cues, to monitor these physiological responses in natural settings.**

6. Natural settings: craving and associated physiological variations

A recent review has examined the combination of EMA and objective ambulatory measures of behavior and physiology in SUD context (Bertz, Epstein et al. 2018). While some studies have examined the detection of drug use by physiological changes (Hossain, Ali et al. 2014, Natarajan, Angarita et al. 2016, Bodin, McIntyre et al. 2017), others have examined the physiological correlates of mental events such as craving or stress. Some studies have examined the physiological correlates of craving in human lab settings (Zhao, Fan et al. 2012, Gullapalli, Natarajan et al. 2019), others have described ongoing protocols in daily-life (Boyer, Fletcher et al. 2012, Shi, Chen et al. 2015), but, to our knowledge, only 4 studies have published results from everyday life (Kennedy, Epstein et al. 2015, Chatterjee, Hovsepian et al. 2016, Carreiro, Chintha et al. 2020, van Lier, Noordzij et al. 2022).

In heroin and cocaine users, HR was significantly greater when participants reported craving than all other random periods measured by continuous monitoring (Kennedy, Epstein et al. 2015). An increase in HR recorded by wearable sensors was also found in patients with alcohol use disorders who reported craving in EMA (van Lier, Noordzij et al. 2022). The development of computational models to estimate craving, *mCrave* model, have been performed by using of wearable sensor during post-quit periods in individuals smoking tobacco (Chatterjee, Hovsepian et al. 2016). This study used features from cardiovascular and respiratory parameters to detect craving and showed an accuracy of classifying craving self-reports of 73%. Across all substances, craving was differentiated from no-craving episodes from accelerometry data by using machine learning algorithm with 76% accuracy (Carreiro, Chintha et al. 2020). This accuracy was increased (82%) when heart rate and EDA data were added in algorithm. However, as mentioned by many authors of these studies, several

limitations can impact the model development, accuracy, and reproducibility (Tackett, Brandes et al. 2019) and temper the impact of these results.

First, craving cannot be identified with a single physiological parameter. At the current stage of knowledge, the use of one single physiological parameter (i.e., HR for (Kennedy, Epstein et al. 2015, van Lier, Noordzij et al. 2022)) may not be enough to identifying this complex phenomenon and a pattern of physiological measures (i.e., combination of HR, EDA and TEMP) maybe more appropriate, especially to determine the consistency and the specificity (Quigley and Barrett 2014). Indeed, the only neuromarker of craving identified to date consists of a pattern of several areas rather than a single structure (Koban, Wager et al. 2023) suggesting that the biology that underlies craving is too complex to be identified just with a single physiologic signal. Secondly, craving must be differentiated from confounding factors. Some variables that could influence the physiological measurements and produce potentially similar responses to craving could interfere with the measurements. Thus, some measures of craving may not be craving specific, but the association of different phenomena, such as stress co-occurring with craving (Kennedy, Epstein et al. 2015, van Lier, Noordzij et al. 2022) (Carreiro, Chintha et al. 2020)). Stress and craving have some physiological similarities (Sinha, Fox et al. 2009), and labeling a no-craving period from observation periods labeled as stress seems inappropriate for differentiating craving from no-craving states. Third, to identify craving, the window time is very important. If it is too short, it might not be enough to identify craving, and would prevent the associated physiology from being captured in its entirety; if it is too long, it might take into account an event other than the craving episode, or the physiological changes might be masked because they would be diluted in too large an observation period. The length of the observation period, from 40 to 180 minutes in some studies, was chosen arbitrarily (Kennedy, Epstein et al. 2015, Carreiro, Chintha et al. 2020, van Lier, Noordzij et al. 2022), while some research suggest that craving episodes could be shorter, between 5 and 30 minutes (Heishman, Singleton et al. 2003, Shiffman, Shadel et al. 2003, Heishman, Saha et al. 2004, Niaura, Sayette et al. 2005, Heishman, Lee et al. 2010). Finally, craving needs to be explored with its fluctuations over time that will need experience-sampling methods (ESM) such as EMA with an adapted length of assessment (De Calheiros Velozo, Habets et al. 2022). The duration of the study must be long enough to capture enough events within individuals (Trull and Ebner-Priemer 2020) (e.g., 24 hours pre-quit and 72 hours

post-quit (Chatterjee, Hovsepian et al. 2016) or 5 consecutive days only (Carreiro, Chintla et al. 2020) could be too short) and to collect sufficient data to be careful about missing data from non-compliance (Jones, Remmerswaal et al. 2019). To assess craving, the use of written-logs, where participants were instructed to report craving, stress or any physical activity in written at any time of the day, without specifying the immediacy of the annotation (Carreiro, Chintla et al. 2020), is at risk for more unreported episodes because data collection relies mostly on retrospective recall that may be prone to recall biases and errors.

The combination of methods (EMA/ESM and physiological data) allows to enrich self-assessments of EMA with objective physiological data and obtain contextual labels to high-frequency time series such as portable sensors (De Calheiros Velozo, Habets et al. 2022). **To our knowledge, no study has proposed a robust methodology to study physiological correlates of craving across substances in daily-life with the combination of EMA and wearable sensor, by using machine learning algorithm.**

7. Key parameters to measure autonomic nervous system changes

The autonomic nervous system (ANS) is a component of the peripheral nervous system and an essential part of the nervous system responsible for the regulation of involuntary physiologic processes. The ANS has the major function to ensure the physiological regulation of body in the face of perturbations by both the external and internal demands of environment (Wehrwein, Orer et al. 2016). It functions involuntarily and is regulated by higher brain structures such as the hypothalamus, brainstem and spinal cord (Buijs and Van Eden 2000). It also interacts with other body systems, such as the endocrine system, to coordinate complex physiological responses (Buijs and Van Eden 2000). The ANS and its division into the sympathetic, parasympathetic and enteric nervous system was originally proposed by Langley (Langley 1903) regarding functional implications of differences in their anatomical organization. Indeed, these sympathetic (SNS) and parasympathetic nervous systems (PNS) are anatomically and functionally distinct and are tonically active. These 2 systems generally work in opposition to each other to maintain the dynamic balance necessary for the proper functioning of the body:

- The **SNS** activates body processes that help in times of need, especially times of stress or danger and in the case of physical activity. This system is responsible for body's

“fight-or-flight” response and helps support intense physical activity. The SNS connects the internal organs and tissues to the brain by spinal nerves. This “fight-or-flight” reaction elicited by SNS that lead to changes throughout body (McCorry 2007);

- The **PNS** is responsible for the “rest-and-digest” body processes and is predominant in calm conditions. The nerve fibers are the cranial nerves, the vagus nerve and the lumbar spinal nerves. This “rest-and-digest” reaction elicited by PNS are (McCorry 2007).

The ANS regulates, by connection with internal organs, physiological parameters such as heart, body temperature, breathing rates or skin conductance. These physiological parameters are commonly used as indicators of psychological arousal. Among the measurable key component of ANS regulation, we find heart rate (HR), electrodermal activity (EDA), accelerometer (ACC) and skin temperature (TEMP), which can be captured by monitoring device such as wearable sensor. Wearable sensors are currently being explored for their potential applications in detecting and managing various clinical conditions, including epilepsy, post-traumatic stress disorder, suicidal tendencies, cardiac arrhythmias, stress, and drug abuse (Fletcher, Tam et al. 2011, Indic, Murray et al. 2012, Beniczky, Polster et al. 2013, Carreiro, Fang et al. 2015, Kennedy, Epstein et al. 2015, Chatterjee, Hovsepian et al. 2016, Carreiro, Chintha et al. 2020, Kaczor, Carreiro et al. 2020, Carreiro, Taylor et al. 2021, Lee, Lee et al. 2021, Shrestha, Stapp et al. 2023)

7.1 Cardiovascular system

Cardiovascular system is a key physiologic parameter to measure the influence of ANS on body and can be described by the heart rate (HR), the heart rate variability (HRV), the inter-beat interval (IBI), the blood pressure and the blood volume pulse (BVP). The ANS precisely and dynamically regulates heart rate, strength of cardiac contractions and other aspects of heart function that can increased by sympathetic-adrenal-medullary (SAM) activation (Frings, Eskisan et al. 2015). The increase of SAM activation leads to increased heart rate and vasodilation. The influence of ANS can be indexed by heart rate variability (HRV). HRV is the fluctuation in the time intervals between adjacent heartbeats (McCraty and Shaffer 2015) and is generated by heart-brain interaction. It is a non-invasive measure of the balance between the cardiac sympathetic nervous system and the parasympathetic nervous system (Jan, Chen

et al. 2019). Changes in the PPG baseline is indicative of the overall amount of blood in the capillary bed. The parasympathetic response is associated with the increased in BVP amplitude (decreased of HRV) that indicate vasodilation of the capillary bed and inversely, a sympathetic response is associated with the decreased in BVP amplitude (increased of HRV) that indicate vasoconstriction of the capillary bed (Shaffer and Ginsberg 2017).

Cardiovascular activity can be captured by Photoplethysmography (PPG) that are a non-invasive optical method that measures changes in blood volume in peripheral vessels using light sensors. It allows to detected changes in light related to heartbeat-induced variations in blood volume. This technique is commonly integrated into heart rate monitoring devices such as Empatica E4®, FitBit®, Samsung Galaxy Watch® that present different signals reliabilities of wich Empatica E4® seems to have the best reliability (van Lier, Pieterse et al. 2020, Ronca, Martinez-Levy et al. 2023) even depending over different conditions (Menghini, Gianfranchi et al. 2019).

7.2 Electrodermal activity

Electrodermal activity (EDA) (also called: galvanic skin responses) is a non-invasive measure of the variations in electrical conductance of the skin (Boucsein, Fowles et al. 2012). Its variation is depending on changes in the levels of sweat ducts. EDA is a physiological index of arousal via SNS innervations of the skin sweat glands, heightened arousal is associated with increases in electrodermal conductance (Critchley 2002, Poh, Swenson et al. 2010, Chen, Jaques et al. 2015). EDA can be captured by using an exosomatic method that consists to apply an external low voltage to the skin which then measures the EDA (Boucsein, Fowles et al. 2012). EDA comprises both the continuous baseline level, known as the skin conductance level (SCL) or tonic component, and the rapid transient responses, called the skin conductance responses (SCR) or phasic component (**Figure 6**) (Caruelle, Gustafsson et al. 2019). The SCL indicates the overall arousal level of an individual in the absence of specific stimuli, while the SCR represents the quick variations in EDA caused by sudden emotional arousal or external stimuli (Benedek and Kaernbach 2010, Boucsein, Fowles et al. 2012). To monitoring EDA and collect good quality of signals, different factors have to take account to avoid artifacts such as the size of the skin that has contact with the electrodes, motion artifacts, density of the sweat gland on the skin... The Empatica E4® seems be the most suitable device currently available

which has good signal quality and the best reliability compared to other devices such as FitBit® (Patel, Park et al. 2012, Menghini, Gianfranchi et al. 2019, Ronca, Martinez-Levy et al. 2023).

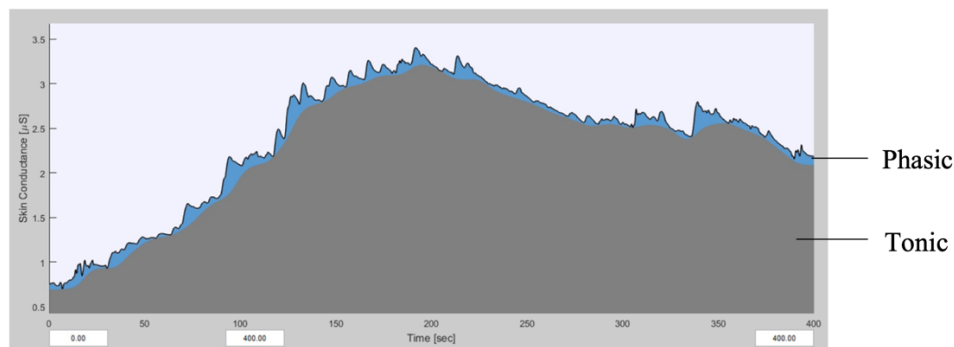


Figure 6 from (Caruelle, Gustafsson et al. 2019). Decomposition of EDA signal into its tonic and phasic components.

7.3 Accelerometer and thermoregulation system

Movement and physical activity (PA) can be used to describe symptoms or characteristics in several psychiatric diseases, include SUDs, such as tremors in individuals who use alcohol, tremors and serotonin syndrome for MDMA, or myoclonus for opioids (Deik, Saunders-Pullman et al. 2012). PA can be captured by three-dimensional accelerometer-based devices (ACC) which integrated in some wearable sensor as like Empatica E4®. ACC-based device is wearing by hands and it is a major area for vasomotor heat loss because this site is rich in arteriovenous anastomoses which adjust blood flow through the skin and thus, play a major role in temperature regulation. ACC signal has allow to differentiate craving from non-craving episode in daily life with a good performance (76%) (Carreiro, Chintia et al. 2020) and to detect convulsive seizure in epilepsy (Beniczky, Polster et al. 2013). A model based on ACC and GPS show an accuracy of 87% to predict the smoking event in participant who wish to quit smoking (Abo-Tabik, Costen et al. 2020).

The thermoregulation system is a complex network that monitors and regulates temperature signals in both the central (core) body temperature, which includes the brain and viscera, and the peripheral (shell) temperatures, encompassing the skin and subcutaneous tissues (Romanovsky 2007). Thus, this is peripheral temperature, the skin temperature (TEMP) that can be measured. The skin temperature, by thermoregulation system, is under control of ANS and can vary based on factors such as ambient temperature, physical activity, emotional

state, and overall health (Greaney, Kenney et al. 2016). When the body is exposed to colder temperatures, the skin's blood vessels constrict to minimize heat loss and maintain core body temperature. Studies show variation of TEMP in SUD context, but only one study has integrated TEMP in signals set analyzed by ML algorithm to differentiate craving from no-craving (Carreiro, Chintla et al. 2020).

8. Hypotheses

Fluctuation of craving at the start of treatment could have an impact on long-term treatment outcome. **We supposed that a better response of craving to treatment at initiation of treatment (i.e.: a more rapid decrease of craving at the beginning of treatment) is associated with a higher probability for remission at long-term.**

Moreover, it would be fundamental to explore the possibility to determine a pattern of physiological changes associated with craving in daily-life. **We supposed that craving is associated with a pattern of physiological changes in daily life from cardiac, electrodermal, accelerometer and skin temperature signals.**

OBJECTIVES

MAIN OBJECTIVE

The main objective was to determine the role of craving in the development of SUD and its severity, its impact on long-term outcomes after initial exposure to treatment and its physiological correlates.

We had 4 *major hypotheses*:

- (1) Craving is involved in the development and maintenance of SUD, i.e., being a central criterion, in DSM-5 network across all substance users;
- (2) The presence of craving is associated with more severity (symptom count) and more use (quantity/frequency).
- (3) A better response of craving to treatment at initiation of treatment (i.e.: a more rapid decrease of craving at the beginning of treatment) is associated with a higher probability for remission at long-term;
- (4) craving is associated with a pattern of physiological changes in daily life from cardiac, electrodermal, accelerometer and skin temperature signals.

To meet our objectives and address our hypothesis we studied craving as a diagnostic criterion (a trait) and a dynamic phenomenon (a state) in two sets (Part I and II) of two studies each (total of 4 studies, considered as 4 individual experiments):

PART I: Explore craving as a diagnostic criterion (trait), first by studying its place and relationship within DSM-5 SUD criteria and by examining its role in the development of SUD.

PART II: Exploring craving as a dynamic phenomenon (state), first by studying the impact of early responses of craving to treatment on long-term outcomes and by investigating its physiological markers in daily life.

PART I: Explore craving as a diagnostic criterion (trait)

STUDY 1:

A first study was conducted to explore craving centrality across SUD based on the study of symptom interactions in cross-sectional network analyses of DSM-5 SUD diagnostic criteria for alcohol, opiates, cocaine, cannabis and tobacco. We used data from ADDICTAQUI Cohort that recruited participants with regular use (2 times per week threshold) and at least one DSM-5 SUD.

This study was completed and published in 2023 in *Drug and Alcohol Dependence*. DOI: 10.1016/j.drugalcdep.2023.109828

Manuscript 1: “The centrality of craving in network analysis of five substance use disorders”

Gauld* C., **Baillet* E.**, Micoulaud-Franchi J.-A., Kervran C., Serre F., Auriacombe M.

*First author

STUDY 2:

A second study was conducted to explore whether craving was an early symptom of SUD and to explore its influence on the development of the disorder. We set-up a one-year longitudinal prospective study among a sample of substance users not in treatment or attempting to access treatment, to evaluate the endorsement of DSM-5 SUD diagnostic criteria every 3 months.

This study was completed and in progress of submission.

Manuscript 2: “Is craving an early marker of SUD? A one-year longitudinal follow-up in an alcohol and tobacco general population user sample not in treatment”

Baillet E., Serre F., Romao C., Moriceau S., Auriacombe M.

PART II: Exploring craving as a dynamic phenomenon (state)

STUDY 3:

A third study was conducted to examine whether trajectory and temporal dynamics of craving over the first 14 days of addiction treatment were associated to long-term outcome. We used, from ADDICTAQUI Cohort and ESM study, an EMA study to collected craving intensity and substance use during the first 14 days of treatment and the prospective follow-up for 5 years or more to assess long-term outcomes.

This study was completed and in progress of submission.

Manuscript 3: “Craving changes in first 14 days of addiction treatment as a predictor of 5 years relapse status”

Baillet E., Auriacombe M., Romao C., Garnier H., Gauld C., Vacher C., Fatseas M., Swendsen J., Serre F.

STUDY 4:

A fourth study was conducted to elaborate a robust methodology to determine the possibility of craving detection based on physiological signals (heart rate, electrodermal activity, skin temperature and accelerometry) captured in daily-life from the combination of EMA and wearable sensor among participants with SUDs. We set-up a 14-day prospective observational study among a sample of substance users not in treatment or attempting to access treatment

This study is in progress of submission.

Manuscript 4: “The Autonomic Craving Signature: a pattern of physiological signals associated with craving in daily-life among tobacco, alcohol and cannabis users with SUD”

Baillet E., Serre F., Monseigne T., Si-Mohammed H., Jeunet C., Auriacombe M.

GENERAL METHODS

1. Population and general procedure

To meet objectives of this PhD work, we have collected data in different population, described after. Inclusion and non-inclusion criteria for each population have presented in **Table 4**. Studies was approved by French Regulation and ethical committee (CNIL, CPP, CEEI/IRB). Informed consent and signed have obtained by all participants before each begin of studies. All tools used in different studies will be described in the next section.

In total, this PhD had examined data of 1,359 participants included in study 1 from ADDICTAQUI Cohort, 39 participants included in study 3 (ESM study), 85 participants included in study 2 (ECEDA study) and 45 participants included in study 4 (BIOEMA study). The ADDICTAQUI Cohort and BIOEMA study are still ongoing.

1.1 ADDICTAQUI Cohort

Addiction Aquitaine Cohort (ADDICTAQUI, Bordeaux, France) included of patients seeking SUD outpatient treatment for at least one DSM-5 Use Disorder Diagnosis (Substance or behavioral addictive) in Care Center of Charles Perrens Hospital in Bordeaux and in Bizia Association in Bayonne (Auriacombe 2019). It's an ongoing prospective cohort, initiated in 1994, which the main objective is to study SUD's patient trajectory seeking treatment in Care Center in Aquitaine Region. It's an ongoing prospective cohort, initiated at 1994, which objective is to explore the trajectory of treatment-seeking patients with SUD in ambulatory treatment center in Aquitaine (France). In context of care, patients received a comprehensive medical diagnosis. The objective of treatment is to initiate or keep abstinence or reduction of use to reduce use-related consequences. The main target of treatment is the loss of control including craving, major predictor of relapse (Auriacombe, Serre et al. 2018b).

All people initiating treatment in one of the two treatment centers are offered participation in the ADDICTAQUI cohort if they were eligible (**Table 4**). They are assessed using standardized instruments in a semi-structured interview conducted by a trained clinical research associate, including the Addiction Severity Index (ASI), Mini International Neuropsychiatric Interview (MINI) and a retrospective craving scale in past 30 days. The interviews are performed at inclusion (at initiation of treatment), at 3-months and every 6-months follow-ups and no-stop excepting if patients want to stop it. The self-surveys are to

complete in the next 7-days of inclusion interviews and are compensated up to 10 euros in vouchers.

The ADDICTAQUI Cohort presented several interests to this PhD:

- (1) To have data already collected since of many years by validated and standardized tools;
- (2) Allow exploration of any criteria included craving in individuals with SUD and links between these symptoms (study 1);
- (3) Allow exploration of the impact of the trajectory of symptoms at the treatment initiation on long-term outcome (study 3).

1.2 ESM study

The ESM study is a prospective observational study. Subjects were recruited at the time of their request for addiction treatment at the Addictology Department of the Centre Hospitalier Charles Perrens and the CHU de Bordeaux. All subjects entering care were assessed during a clinical interview to collect individual characteristics such as socio-demographic features and dependency criteria using the ASI and MINI. According to specific criteria (**Table 4**), subjects are offered to participate in ESM study. After signing the informed consent form, the subjects received a second interview to assess the variables that would enable them to personalize the questionnaires in their daily lives. Each patient's referring physician was contacted to find out the start date of treatment, as well as the substance on which the start of treatment would be focused in the case of polyaddiction. Subjects were also asked to complete a series of self-questionnaires (ERS, BAI, BDI, TCI). A third appointment was scheduled on the day the treatment began. Each subject was then given a PDA and trained in its use during a 30-minute interview, which also served to ensure that all questions had been properly understood. Urine toxicity and blood alcohol levels were determined. During the 14 days of assessment in daily life, subjects were seen at the center once or twice a week to ensure that the study was running smoothly, and to perform urinary toxin and blood alcohol determinations. At the end of the two-week assessment period, a final appointment was scheduled to collect the equipment and retrospectively evaluate the treatments and services received during the study, using the TSR-14. Urine toxin and blood alcohol tests were also performed.

The ESM study presented several interests to this PhD:

- (1) To have data already collected by EMA protocols;
- (2) Allow exploration of the trajectory of craving at the treatment initiation (study 3).

1.3 ECEDA study

The Addiction team of SANPSY Laboratory is the principal investigator of ECEDA study which University of Bordeaux is the promotor. This study supported by National Institute of Cancer and Research Institute of Public Health (INCa-IReSP_15746) which the recruitment was performed by KANOPEE Application that has been developed by my host laboratory (Auriacombe, Fournet et al. 2021). KANOPEE is a smartphone application accessible to the general population developed during the COVID19 pandemic period. The application uses an Embodied Conversational Agent (ECA) to assess alcohol, tobacco and cannabis consumption of users with standardized screening tests (Auriacombe, Moriceau et al. 2018). According to specific criteria (**Table 4**), application users are offered to participate in ECEDA study by a smartphone notification. If they accepted to participate, they are offered to send their contact information et were recalled by the following.

The ECEDA study is a one-year prospective longitudinal study which the objective is to assess the evolution of DSM-5 SUD diagnostic criteria over time in KANOPEE users screened as non-problematic alcohol, tobacco or cannabis users (Mayfield, McLeod et al. 1974, Auriacombe, Moriceau et al. 2018). Participants were assessed individual interview at inclusion (ASI – Substances Part; MINI – Use Disorders; Craving scale) and every 3-months using the same tools, during one year (**Figure 7**). All interviews were only by phone. The participants received a voucher of 10 euros at inclusion, at 6-months (if they have answered at 3 and 6-months follow-ups) and at 12-months follow-up (if they have answered at 9 and 12-months follow-ups).

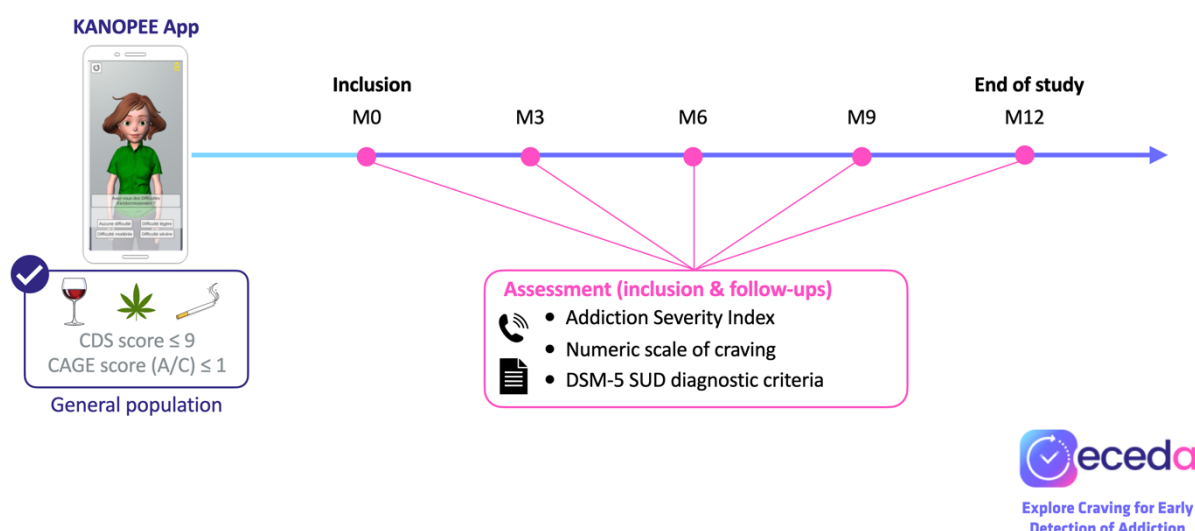


Figure 7. Experimental design of ECEDA study

The ECEDA study presented several interests for the PhD:

- (1) Collect data among individuals not in treatment who use reinforcing substances to explore DSM-5 SUD diagnostic criteria including craving (study 2);
- (2) Explore the trajectory of craving among individuals who use reinforcing substances (study 2);
- (3) Explore the evolution of diagnostic criteria of reinforcing substances on one-year longitudinal study (study 2).

1.4 BIOEMA study

The Addiction team of SANPSY Laboratory is the principal investigator of ECEDA study which University of Bordeaux is the promotor. This study supported by National Institute of Cancer and Research Institute of Public Health (INCa-IReSP_15746) which the recruitment was performed in 2 populations: among individuals not in treatment and in ADDICTAQUI Cohort. Funding for the EMA study was provided by Research Grant AAP-19-ADDICTIONS-16 from the public health research institute (IReSP) and Aviesan Alliance as part of the call for research projects to combat addiction to psychoactive substances to Marc Auriacombe and Fuschia Serre.

The BIOEMA study is a 14-day transversal observational study in daily-life uses EMA method coupled with wearable sensor. The main aim is to identify physiologic variations

associated craving episodes in natural environment among individuals presented a SUD for one substance (alcohol, tobacco and cannabis) and depending of consumption context: active use (Not in treatment) or treatment-seeking (Treatment Center).

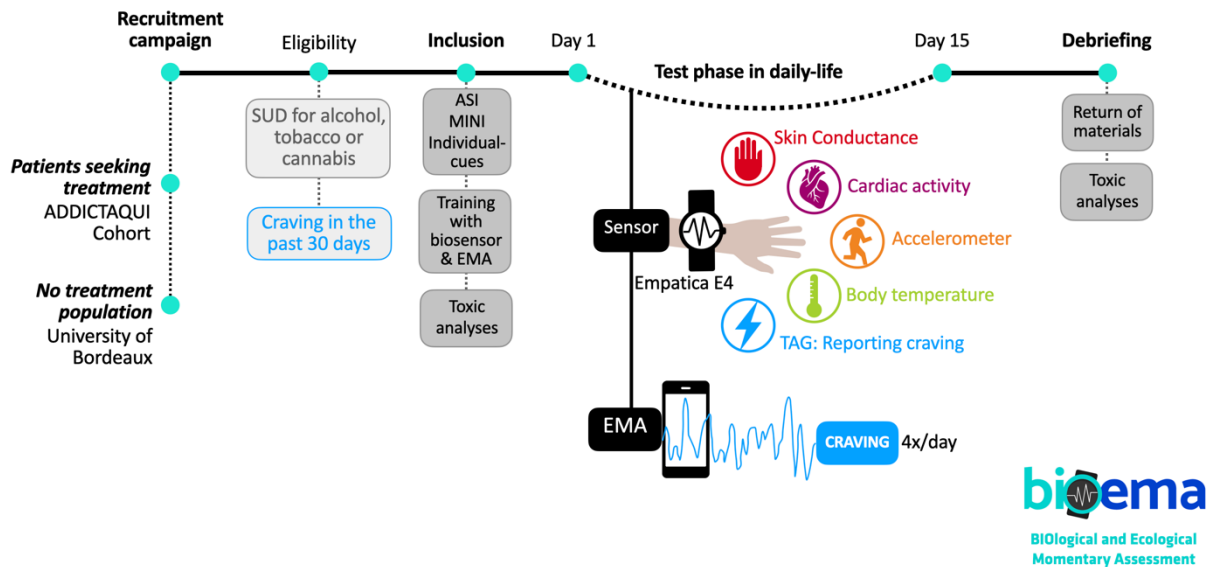


Figure 8. Experimental design of BIOEMA study.

A recruitment campaign on social networks and at University of Bordeaux (**Appendix 2**) was used to recruit eligible individuals who use substances and not in treatment. Individuals that interested by our study, a short interview by phone was performed to verify their eligibility. Eligible individuals in the ADDICTAQUI Cohort are offered participation in the study (**Table 4**). As describe in the **Figure 8**, participants were assessed in individual interview at inclusion (ASI, MINI, Craving scale). After, they received a second interview allowing training in the use of the CUSEMA application and the completion of the Associated situations Questionnaire (ASQ) which identifies the subject's personal cues.

Financial compensation was provided as a function of number of electronic surveys completed, with a maximum of 100 euros for participants who completed 75% or more of the electronic assessments and with a maximum of 100 euros for participants had to wear the sensor at least 6 hours/day.

The BIOEMA study presented several interests for the PhD:

- (1) Collect real-time ecological data, using the EMA method, to assess fluctuations in various variables, including craving (study 4);
- (2) Collect real-time physiological data, using wearable sensor, to assess changes of physiological arousal (heart rate, electrodermal activity...) (study 4).

Table 4. Inclusion and non-inclusion criteria for each population.

Population	Subject number	Inclusion criteria	Non-inclusion criteria
<i>ADDICTAQUI Cohort</i>	1,359	(1) ≥ 18 years (2) Treatment-seeking for reinforcing substance or behavior (ASI-DAQ14) (3) Have a SUD diagnosis according to the DSM-5	(1) Disability, somatic or psychiatric condition or severe cognitive impairment that is incompatible with understanding the tools or prevents data collection (2) Difficulty reading, writing or understanding French
<i>EMA study</i>	39	(1) From 18 to 65 years (2) Have a SUD diagnosis according to the DSM-IV for alcohol, tobacco, cannabis, cocaine or opiate	(1) Disability, somatic or psychiatric condition or severe cognitive impairment that is incompatible with understanding of EMA study or PDA use
<i>ECEDA study</i>	85	(1) ≥ 18 years (2) Alcohol, tobacco and/or cannabis users in the past 12-months (3) CAGE Score ¹ (Alcohol and/or Cannabis) ≤ 1 and/or CDS Score ² ≤ 9	(1) Not reachable by phone (2) Disability, somatic or psychiatric condition or severe cognitive impairment that is incompatible with understanding the tools or prevents data collection (3) Difficulty reading, writing or understanding French
<i>BIOEMA study</i>	45	(1) ≥ 18 years (2) Have a SUD diagnosis for alcohol, tobacco, or cannabis according to the DSM-5	(1) Have a low clinical insight to HAISm (2) Disability, somatic or psychiatric condition or severe cognitive

¹ Cut Down, Annoyed, Guilty, Eye-opener

² Cigarette Dependence Scale

		<p>A. No treatment population: No treatment-seekers for the reinforcing substance</p> <p>B. Treatment center (CSAPA): Treatment-seekers for the reinforcing substance</p> <p>(3) Have experienced craving for this substance in the past 30-days</p> <p>(4) In the case of polyaddiction, have identified a main substance that will be the primary focus substance</p>	<p>impairment that is incompatible with understanding the tools or prevents data collection</p> <p>(3) Have a cardiovascular disease</p> <p>(4) Have a non-dominant upper extremity limitation</p> <p>(5) Have obvious skin conditions, such as eczema or psoriasis, that may interfere with the use of the sensor and affect its conductivity</p> <p>(6) Being pregnant</p>
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2. Tools

2.1 Hetero-questionnaires

2.1.1 *Addiction Severity Index (ASI)*

The ASI is the most using instrument in the world to evaluate the users of reinforcing substances or behaviors (McLellan, Kushner et al. 1992). The test consists of a 40-90 minutes semi-structured interview by a specially trained assessor. He collects information's about 7 domain that could be affected by use: medical status, employment/financial resources, substances and behaviors, family and social relationships, legal status, psychological status. According to theses information, the assessor has a severity score in each domain (0 to 9), a more or equal score than 4 indicates the need for the domain-specific treatment. Three-day test-retest and inter-rater fidelity are very good. The severity scores are a valid measure of the subject's condition. The version modified ASI (m-ASI), to take account the tobacco use, the gambling behavior and the others addictive behaviors have been using in this project (Denis, Fatséas et al. 2016). The ASI can perform at inclusion (basis ASI), then repeated over time (Follow-up ASI). Since November 2019, 2 items have been added follow-up ASI surveys to assess the modification of use since the last ASI: abstinence (total, more than 2 weeks or none); regular use (present or absent) at a rate of 2 days of use per week over 2 consecutive weeks.

For the study 3, the “relapse” variable has been modeled with “consumption in the past 30-days” variable of available last ASI and the “inclusion substance” variable of EMA study at treatment-initiation. Participants were assigned to the “relapse” group if they reported at least 1 day of use of the inclusion substance in the last follow-up ASI. Participants who had not reported use if the past 30 days of the inclusion substance in the EMA study were assigned to the “remission” group.

2.1.2 Mini International Neuropsychiatric Interview (MINI)

The MINI is a 10- to 25-minute structured hetero-questionnaire to explore diagnoses of the 17 major DSM-IV Axis I psychiatric disorders, including substance abuse (Sheehan, Lecrubier et al. 1998). The validity, sensitivity, and reliability of this tool have been demonstrated (Sheehan, Lecrubier et al. 1998). Two assessment periods are explored: current (last 12 months) and past (lifetime). Across studies, we used a version of the MINI adapted to the changes introduced in the DSM-5 for use disorder (UT) (American Psychiatric Association 2013). The severity cutoffs applied were those of the DSM-5: 2-3 mild TU, 4-5 moderate TU, 3 6 severe TU for substances.

For the study 1 et 2, we used these DSM-5 SUD diagnostic criteria.

2.1.3 Retrospective craving evaluation scale

The numerical craving assessment scale was developed by the SANPSY laboratory and measures the number of days (frequency) that the subject has experienced craving over the last 30 days preceding the interview, for all substances or behaviors used regularly by the subject. The average and maximum intensity are assessed using a numerical scale ranging from 0 (no craving) to 10 (extreme craving). Craving is defined by the evaluator as "an irrepressible urge to use and/or a disturbing desire to use and/or the occurrence of obsessive thoughts centered on the object of use".

2.1.4 Treatment Record

The pharmacological treatments used by the participants are recorded on a form which is systematically completed at the time of the ASI. It allows for the quantitative collection

(number of days, dosage, prescribed...) of treatments taken by participants over the last 30 days for addiction problems, other psychiatric pathologies and/or somatic problems.

2.1.5 Associated Situations Questionnaire (ASQ)

The ASQ is a hetero-questionnaire that was specifically designed for the EMA study and has been used in previous studies (Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2015). It allows for the identification of each participant's individual cues; that is, cues that are unique to them, associated with their use of the primary problem substance and/or likely to trigger craving or use. The first part of the interview explores the subject's usual context of use according to five modalities: the place, the environment, the time, the emotions and the material used to consume. For each modality, the participant chooses the proposals that best correspond to his or her consumption habits from a standard list (corresponding to the one presented during the daily life evaluation). The subject can then propose as many contexts or situations that are specific to him/her.

2.1.6 Debriefing

The debriefing interview takes the form of a hetero-questionnaire and was created for the EMA studies. An adaptation of the Substance/Alcohol section of the ASI, retrospectively collects substance use and practice of addictive behaviors during the 14 days of EMA. A question was added to assess the duration of longest abstinence. Another question assessed changes in dosages of prescribed medications for addiction. Retrospective craving over the 14 days (Craving-14 days) is also recorded in terms of the number of craving days over 14, and the average and maximum intensity on a numerical scale (0 no craving - 10 extreme craving) (adapted version of the 30-day scale). A follow-up was added one month after the debriefing interview, which includes an adaptation of the Substance/Alcohol section of the ASI. It retrospectively collects the problems experienced (including craving) with the EMA study's inclusion substance in the past 30 days, how disruptive/preoccupying these problems were, and how much the participant would like help (additional for participants already in treatment).

2.1.7 Montreal Cognitive Assessment (MoCA)

The MoCA allows the identification of mild cognitive dysfunctions in a large number of cognitive functions: executive functions, visual-constructive abilities, language, memory, attention, concentration, abstraction capacity, calculation, spatio-temporal orientation (Nasreddine et al., 2005). This evaluation, which takes 10 to 15 minutes to complete, makes it possible to determine, according to the score obtained and the level of study, the presence of severe cognitive impairment (score less than 10/30), moderate impairment (score between 10 and 17/30), mild impairment (score between 17 and 26/30) or the absence of cognitive impairment (score greater than or equal to 27/30). An additional point is awarded if the subject's level of education is less than or equal to the baccalaureate level (12 years of study).

2.2 Self-questionnaires

2.2.1 Diary journal

The diary journal is a book given to each participant that allowed both for the participant to have information about study and functioning of EMA and sensor devices (*How do I connect my sensor? When do I press the button on my sensor? What should I do when I feel craving?...*) and for the assessor to collect information about participants' days. The aim of the diary journal is to collect any main information that led to physiologic changes. Indeed, the diary journal allows us to collect: (1) sport practices or activity as sexual activity, sport session, walk, bike...; (2) intake of any treatment (links to addiction treatment or not); (3) the moment where participants have felt craving and pressed on button with intensity of craving. Participants were asked to complete the diary daily and as much as possible.

2.2.2 Hanil Alcohol Insight Scale – modified version (HAIS-m)

The HAIS is a self-administered questionnaire that quantitatively and qualitatively assesses the clinical insight that individuals have about their alcohol addiction (Kim, Kim et al. 1998). It takes about 10 minutes to complete. The original version has a good or very good psychometric quality (internal validity: Cronbach $\alpha = 0.89$; sensitivity: 76.9 to 100% and specificity: 83.3 to 94.9%) (Kim, Kim et al. 1998). The French version has been validated and has comparable psychometric properties (Dandaba, Ebrahimighavam et al. 2020). It consists of 19 items divided into three categories: (1) "Minimization of alcohol problems" (MPA); (2)

"Recognition of loss of control" (RPC); and (3) "Awareness of a problem with alcohol and the need for treatment" (CPNT). The total score ranges from -18 to 20. For the purposes of the PhD, the French version was adapted to be used regardless of the type of addiction (substance or behavior), as well as for individuals outside of the treatment setting (No treatment population).

2.2.3 Cigarette Dependence Scale (CDS) (in KANOPEE App)

Kanopee users were proposed to respond Five-item Cigarette Dependence Scale (CDS-5) by an embodied conversational agent (ECA). The CDS-5 evaluates tobacco dependence and has been validated and considered as a reliable measure (Etter, Le Houezec et al. 2003). Scores vary from 5 to 25, and the threshold score for dependence was set at 9 in accordance with the DSM-5 (Auriacombe, Moriceau et al. 2018).

For the study 2, Kanopee users with score less than or equal to 9 were offered to participate at ECEDA study with a notification on their smartphone.

2.2.4 Cut Down, Annoyed, Guilty, Eye-opener (CAGE) questionnaire

Kanopee users were proposed, such as for tobacco, to respond Cut Down, Annoyed, Guilty, Eye-opener (CAGE) questionnaire by an ECA. The CAGE has been validated and considered as a reliable measure (Bush, Shaw et al. 1987). Scores varying from 0 to 4 in accordance with DSM-IV and DSM-5 and the threshold score for a problem with alcohol was a score >1.

For the study 2, Kanopee users with score less than or equal to 1 were offered to participate at ECEDA study with a notification on their smartphone.

2.3 Daily-life devices

The daily-life devices were the combined use of wearable sensor and Ecological Momentary Assessment method. This mixed and personalized methods allow use to collect both physiological activities data and emotional, context or use data, exclusively in natural environment of participants.

2.3.1 Wearable sensor

The E4® sensor (Empatica Inc., Cambridge MA, USA) is a non-invasive wearable device, in the form of a wristband, which allows the acquisition of physiological data in real time and continuously (**Figure 9**). This device is primarily intended for research purposes with validity compared to a reference device (Enewoldsen 2016, Schuurmans, de Looft et al. 2020, van Lier, Pieterse et al. 2020). Participants were asked to wear the sensor every day from the time they woke up until they went to sleep.



Figure 9 adapted from <http://empatica.com>. The E4-wristband-Empatica, overview of sensors.

The sensor allows to signal an event (by the pressure of a button in the sensor) and to collect of the following physiological data that are as surrogate markers for changes in SNS arousal:

- **Electrodermal activity (EDA)** measured in microSiemens (μS) and sampled at 4Hz. EDA is recorded via an electrodermal sensor that measures constant variations in certain electrical properties of the skin such as the galvanic response of the skin;
- **Three-dimensional acceleration (ACC)** measured in gravity (g) [-2g, 2g] where 1 g is equivalent to the Earth's gravitational acceleration, i.e., approximately 9.81 m/s^2 . Sampling frequency of 32Hz. CCA was measured via a 3-axis (x, y, z) accelerometer that captures motion-based activities

- **Skin temperature** measured in degrees Celsius (°C): sampling rate at 4Hz via an infrared thermopile that allows the reading of peripheral skin temperature
- **Blood volume pulse (BVP)** have not a unit of measurement because it's derived from the combination of two different measures of the amount of light that is reflected and goes back to the sensor. The BVP is sampled at 64Hz and is recorded by photoplethysmography from which we can deduce the variability of the heart rate, the heart rate, the inter-beat interval.

The sensor is connected via Bluetooth to the "E4 real-time" application (available on Play Store and Apple Store) on the participant's phone. The data is stored on a secure cloud until the recording stops and then can be downloaded directly to the E4 Connect site by the evaluator.

For the study 4, participants were asked to report when they experienced craving, regardless of intensity, by pressing the sensor button (TAG).

2.3.2 *Ecological Momentary Assessment*

Participants are provided with a smartphone for the duration of the study which data are anonymous and crypted. The questionnaires are presented 4 times a day in a random way on a fixed time slot of 14 hours according to the habits (sleep/wake) of the subject, and according to a frequency defined beforehand. This strategy is particularly interesting because it allows to cover the variations of the variables of interest over the whole day. The electronic questionnaires are available for 20 min from the first sound signal and spaced at least 1 hour apart, i.e., approximately 1 questionnaire every 3h30. The response time for a questionnaire is approximately 3 to 5 minutes.

The questionnaires are adapted to the main addiction defined for each individual according to item DAQ30/31 of the ASI (and the medical opinion in treatment center), and in case of doubt (e.g., poly-addiction) the choice is made on the diagnostic severity at the MINI: alcohol, tobacco, cannabis. Some questions assess the situation in which the subject is at the time of answering: location, social environment, activities, emotions, stress level, insight etc. Other questions assess the period that has elapsed since the last questionnaire was

completed: use, intensity of craving, standard and personal cues (collected by the ASQ), use of medication prescribed for the addiction, withdrawal symptoms, or difficulty in resisting the craving; other uses (substances) are also assessed. During the first assessment of the day, questions assess sleep and night-time use. The evening questionnaire collects the amount, number of times and/or duration of use of the main addiction and each other substance used during the day.

For the study 4, craving is assessed over a retrospective period using one item:

- "Since the last questionnaire, have you felt a desire to use [*main addiction*]?" (numeric scale from 1 (no desire) to 7 (extreme desire));

2.4 Biological assay

Biological assays allow an objective measure of use and an assessment of coherence between use reported by participants and the results of biological assays on this use, although any use can't be verified.

2.4.1 Urinary assay

A urine sample is collected in a controlled manner to detect the presence of various substances in the urine: morphine, methadone, buprenorphine, tramadol, cocaine, benzodiazepines, cannabis (THC), amphetamines, ethylglucoronide (alcohol). The reading of the results is almost instantaneous thanks to the use of collection pots with integrated strips.

2.4.2 Carbon monoxide breath tester

The carbon monoxide breath tester provides a measurement in parts per million (ppm), it gives an indication on the degree of intoxication of the smoker, consequence of his tobacco consumption. Pollution can also be responsible for a few ppm. The result is instantaneous.

2.4.3 Ethylometer

Electronic ethylometer allowed us to measure the alcohol (ethanol) rate in breath expired (g.L^{-1}). For the use, there is a disposable tip on the device and the participant should blow directly into it, until the sound signal stops. The value is displayed on the screen immediately.

3. Statistical modeling

3.1 Study of craving in relation to other DSM-5 SUD diagnostic criteria

We performed a network analysis to explore the role of craving in the development and the maintenance of SUD, i.e., the centrality of craving, and to explore its relationship with the other symptoms of DSM-5 SUD. In this network, the 11 symptoms of addiction are DSM-5 SUD diagnostic criteria. All criteria have been described in **Table 2**.

First, we conducted an estimation to build the network graphical representations (Fruchterman-Reingold algorithm) of each of the five SUD, with a connection between any two diagnostic criteria (symptoms) if these diagnostic criteria were present in the same patient and with nodes depicted closer together more strongly related. We used an Ising model (an undirected network of partial correlation coefficients for binary data) that brings pairwise relationships (conditional dependence relationships) between diagnostic criteria and a network regulation (Epskamp, Borsboom et al. 2018).

Then, we analyzed centrality by quantifying the structure of these five networks, at a local level, by four metrics (Bringmann, Elmer et al. 2019) of network analysis:

- **Strength:** Node strength is the sum of the weights of the edges attached to that node. The weighted number of connections for a given node, and the degree to which it is connected with all the other nodes of the network can be computed (Barrat, Barthélemy et al. 2004). A criterion has high strength centrality if this criterion is highly connected to all the other criteria. In the rail network metaphor, a city has high strength if it is connected to an extremely large number of other cities, e.g.: Washington in the USA.
- **Closeness:** The closeness of a node is computed according to the shortest path length measure and is inversely proportional to the shortest mean distance from all the other nodes (Boccaletti, Latora et al. 2006). Closeness centrality indicates the average distance of a node from all other nodes in the network and is computed as the inverse of the weighted sum of shortest path lengths to a given node from all other nodes in the network. A criterion has high closeness centrality if the criterion can be connected shortly to other criteria (Richetin, Preti et al. 2017, Smith, Lee et al. 2017, Bringmann, Elmer et al. 2019). Using the rail network

metaphor, a city has high closeness if it is central compared to many other cities, i.e.: it is “close” to many others, like Kansas City which is very central in the USA.

- **Betweenness:** The betweenness of a node computes the degree to which a given node acts as a “bridge” connecting different parts of the network, thus reflecting the degree to which it controls the flow of information across the network. The betweenness centrality of a node equals the number of times that it lies on the shortest path length between any pair of other nodes. A criterion has high betweenness centrality if the criterion can influence the connection between non-adjacent (i.e., not directly connected) criteria, thus acting as gatekeeper (Bringmann, Vissers et al. 2013, Bringmann, Elmer et al. 2019). In the railroad network metaphor, a city has high betweenness if it is necessary to transit through that city to reach other cities, like Las Vegas, which should be passed through on the route between San Francisco and New York City.
- **Expected Influence:** The expected influence of a node is computed to improve the measurement of centrality of the nodes in a network (Robinaugh, Millner et al. 2016). It is computed as the sum of all edges which extend from a given node, accounting for both positive and negative correlation values with regard to the entire network. A criterion with high Expected Influence has an influence on the criteria network based on its positive correlations, negative correlations being corrected by this centrality measure. In the railroad network metaphor, a city has a high expected influence if it is connected to an extremely large number of connected neighboring cities, considering possible negative correlation values between cities.

Centrality can be understood to reflect how connected and thus potentially clinically relevant a diagnostic criterion is in a network (via paths through other diagnostic criteria, intervening on a highly central diagnostic criteria, other nodes will be both directly and indirectly affected). Measures of centrality are given with standardized Z-scores, i.e., standardized coefficients calculated by subtracting the mean and dividing by the standard deviation for each observation.

Then, because our sample size according to type of substances being heterogeneous, we analyzed robustness in terms of stability of diagnostic criteria network centralities, with the calculation of the CS-coefficient.

Finally, the five individual networks have been compared to each other with a network comparison tool providing significance indices evaluating the differences between each network.

3.2 Study of craving on evolution of SUD

Data analyses collected longitudinally during one-years performed first by associations (linear regression and Kruskal-Wallis tests), then by Hierarchical Linear and non-linear Model (HLM) (Raudenbush, Bryk et al. 2005).

3.2.1 *Association between the addiction severity and craving at baseline and over time*

Firstly, we have explored the number of criteria (except craving criterion) at 12-months follow-ups reported by participants with (presence) or without (absence) craving at baseline with linear regression controlling for status of the SUD criteria at T0.

Secondly, to take account the variability of craving over time which was collected at baseline and at each follow-up during one year, we modeled persistence of craving by its trajectory overtime to differentiate groups with stable (positive or negative) or unstable craving endorsement. Then, these trajectories of craving were used to assess the impact on the addiction severity (DSM-5 criteria count, frequency/quantity of use) at the last follow-up. Craving groups were based on its presence vs. absence between baseline and the other follow-up available:

- **Always Craving Group (C_{Always}):** if craving was endorsed at all available assessment (0M, 3M, 6M, 9M, 12M);
- **Never Craving Group (C_{Never}):** if craving was not endorsed at all available assessment;
- **Sometimes Craving Group ($C_{\text{Sometimes}}$):** if craving was endorsed inconsistently overtime.

Craving group has been established only if there is at least one available follow-up. Number of endorsed criteria (except craving criterion) and quantities used (number of day and quantities per day) were compared with Kruskal-Wallis test between each group. Post-hoc analyses for multiple comparison were realized between each group with a Dunn's rank-sum test.

3.2.2 *Hierarchical Linear and non-Linear Modeling*

To test the direction of these potential associations by taking into account each craving assessments and the nested nature of the data, we used hierarchical linear and non-linear modeling (HLM) (Raudenbush, Bryk et al. 2005) that involved within-person variance for craving, substance use and the number of criteria as well as between-person variance for clinical and sociodemographic characteristics. Thus, we examined (1) whether craving at T0 was prospectively associated with more criteria, frequency of use and quantity of use at the next assessment and (2) whether craving over time at T0 was associated with more criteria, frequency of use and quantity of use at the next assessment. For (1), a random coefficient regression model tested the influence of craving at T0 on the number of criteria or the frequency of use at T0; and for (2) a random coefficient regression model tested the influence of craving at T0 on the number of criteria or the frequency of use at T1 (controlling for status of the SUD criteria or the frequency of use at T0), then the cross-level interaction of time was tested on this association. The variable of SUD criteria number excluded craving criterion. The number of criteria and the frequency/quantity of use were time-lagged for prospective associations. Each model was performed separately between alcohol and tobacco samples. Continuous variables were group-centered (i.e., centered around the individual's own mean) for within-person variables, and grand-centered (around the sample average) for between-person variables.

3.3 Study of trajectory of craving at treatment initiation on long-term outcomes

Data analyses collected with EMA method in daily-life performed by Hierarchical Linear and non-linear Model (HLM) (Raudenbush, Bryk et al. 2005) that allow to take account the multilevel structure of the data that involved within-person variance for day in EMA protocol, craving and substance use, as well as between-person variance for clinical and

sociodemographic characteristics. Then, we used metrics of dynamic of craving that allow to explore how the symptom fluctuate (magnitude, fastness of change...).

3.3.1 Hierarchical Linear and non-linear Model

The variability of craving was assessed at 3 different levels: the person-level (*level 3*), the day-level (*level 2*) and the assessment-level (*level 1*) (Cleveland, Knapp et al. 2021). To estimate the amount of variability of craving and their level and before exploring hypotheses, a *three-level unconditional model* was done, represented by the equation (1):

$$\begin{aligned} \textbf{Level 1: } \text{Craving}_{mi} &= \Psi_{0ti} + \varepsilon_{mti} \\ \textbf{Level 2: } \Psi_{0ti} &= \pi_{00i} + e_{0ti} \\ \textbf{Level 3: } \pi_{00i} &= \beta_{000} + r_{00i} \end{aligned} \tag{1}$$

Where: Craving was estimated for participants i , on days t , in the assessment period m . Fixed effect β captures the sample-level mean craving with π capturing the mean for person i and Ψ capturing the person's mean craving on day t . Individual variations were captured by the random effects r_{00i} , e_{0ti} , ε_{mti} , at the person, day and assessment levels respectively.

To examine the first hypothesis that relapse is associated with difference in time-dependent evolution of craving at the beginning of treatment, first a random coefficient regression model tested the influence of time (day in study) on craving intensity in EMA study. Then the cross-level interaction of relapse was tested on this association. This model is represented by the equation (2):

$$\begin{aligned} \textbf{Level 1: } \text{Craving}_{mi} &= \pi_i + \Phi(\text{Time} * i) + \varepsilon_{mi} \\ \textbf{Level 2: } \pi_i &= \beta_{00} + \beta_{01} * (\text{Relapse}) + r_{0i} \\ \Phi_i &= \beta_{10} + \beta_{11} * (\text{Relapse}) + r_{1i} \end{aligned} \tag{2}$$

Additional analyses were conducted to explore if relapse status was associated with difference in craving intensity, substance use (primary substance, and other substances use) and in the craving-use relationship at beginning of treatment. For this, prospective association

between craving at one time, and primary substance use at the next assessment was explored. Then, relapse status was added as an interaction term.

In all HLM analyses, continuous variables were group-centered (i.e., centered around the individual's own mean) for within-person variables, and grand-centered (around the sample average) for between-person variables. These time-lagged analyses examined within-day (and not across-day) associations. Concerning missing data (NA) (20.1% of EMA data), Kendall's τ tests were conducted to evaluate whether NA were missing completely at random (MCAR), missing at random (MAR) or not missing at random (NMAR) (Pugh, Brown et al. 2022). No correlation was found between craving NA and day on study ($Z=1.106$, $\tau=.08$, $p=.095$), assessment number ($Z= -1.472$, $\tau=-.03$, $p=.141$), primary substance use ($Z=1.393$, $\tau=.04$, $p=.164$), other substance uses ($Z=.817$, $\tau=.02$, $p=.414$), suggesting that missing data on craving were MCAR/MAR. Thus, NA were handled by excluding that particular observation from analyses. Due to our limited sample size in each primary substance group, analyses were performed in the entire sample, regardless of the substance. An alpha level of .05 was used in all analyses.

3.3.2 Dynamic metrics

To explore if relapse is associated with difference in craving changes at the beginning of treatment, we calculated the instability, variability and inertia metrics of craving. The craving *instability* was obtained by calculating average within-person root mean square of successive differences (rMSSD) (Neuman 1941, Jahng, Wood et al. 2008) of craving intensity within-day, the craving *variability* by the within-person Standard Deviation (SD), and the craving *inertia* by means of average within-person autocorrelation (AR1) of craving at time t and craving at time $t-1$. Associations between relapse status and each craving metrics were tested with logistic regression, while controlling the average craving intensity.

3.4 Study of physiologic identification of craving predictive of use in daily-life

To identify physiological signal associated with craving in daily-life, it was essential to have a robust pipeline for the automation of data analysis. The processes for the signal analysis pipeline were be as follows in **Figure 10**.

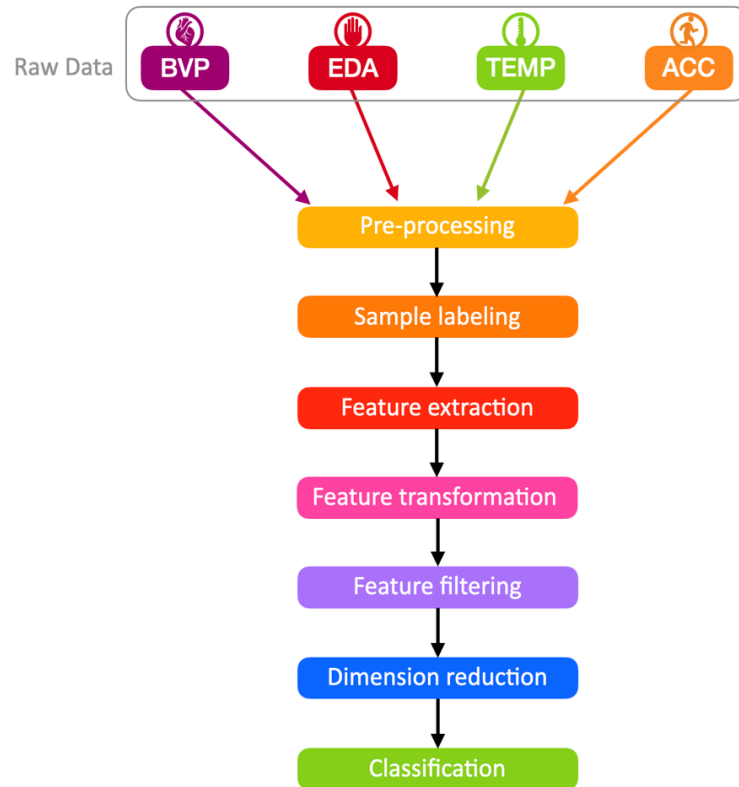


Figure 10. Signal processing methodology of BIOEMA study analysis.

3.4.1 Data pre-processing

The representation and the quality of dataset can influence the success of data mining. The data preparation step is very important to eliminate redundant and related or noisy, and unreliable information in dataset. The device of Empatica E4® integrates algorithm of cleaning. Thus, this step is relatively short and consists to identifying and removing errors or inconsistencies from a dataset (Alexandropoulos, Kotsiantis et al. 2019).

3.4.2 Sample labeling

In our study, craving was assessed by 2 methods: sensor and EMA.

For the sensor, participants were instructed to press the sensor button ('TAG') of sensor when they felt craving, regardless of intensity. **For the EMA**, craving was assessed every 3 hours every day with the following question: "Since the last questionnaire, have you felt a desire to use [main addiction]?". The response was the intensity of craving, ranging from "No desire" (intensity 1) to "Extreme desire" (intensity 7).

Both methods enabled us to sort our samples in Class of craving. Each class were either coherent or incoherent depends of craving report both sensor and EMA.

- **Consistent classes:** consistency on the ratio of craving report between the sensor and the EMA (**Figure 11**):
 - **Class 0 – No-craving period:** no craving reported on sensor (no-TAG) and no craving reported in EMA (intensity 1);
 - **Class 1 – Craving period:** craving reported on the sensor (TAG) and craving reported on the EMA (intensity>4 corresponding to the average of the craving measurement scale).

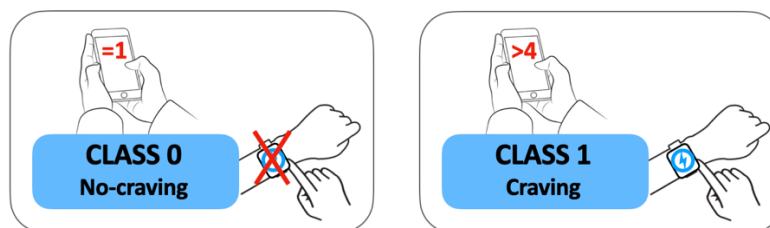


Figure 11. Class selection criteria into consistent classes.

- **Inconsistent classes:** inconsistency on the ratio of craving report between the sensor and the EMA (**Figure 12**):
 - **Class 2:** no craving reported on sensor (no-TAG) and craving reported on the EMA (intensity>1)
 - **Class 3:** craving reported on the sensor (TAG) and no craving reported in EMA (intensity 1);
 - **Class 4:** craving reported on the sensor (TAG) and craving reported on the EMA (intensity=2 or 3). Although craving was reported on EMA, it was of relatively low intensity. Our craving class had to be strictly high intensity, so class 4 was classified as inconsistent.

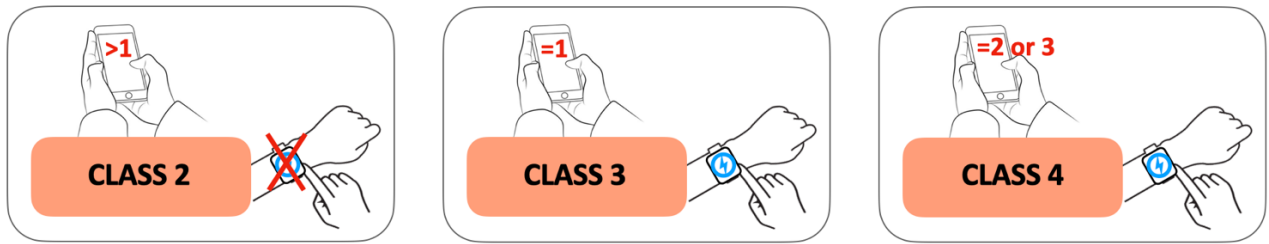


Figure 12. Class selection criteria into inconsistent classes.

All physiological data were selected by class (0, 1, 2, 3 or 4). If some data (EMA or biosensors) were not available, they were not included in the subsequent steps of our analysis.

For feature selection, we used **epochs of 10 minutes** to create our samples by class:

- Consistent classes:
 - Class 0 – no-craving period: epochs of 20 minutes *randomly* in the EMA period corresponding;
 - Class 1 – craving period: epochs of 10 minutes *before and after* the TAG in the EMA period corresponding.
- Inconsistent classes:
 - Class 2: epochs of 20 minutes *randomly* in the EMA period corresponding;
 - Class 3 & 4: epochs of 10 minutes *before and after* the TAG in the EMA period corresponding.

At this step, each sample of epoch of 20 minutes belongs to a specific class and the subsequent steps will be performed only on these samples.

3.4.3 Feature extraction

Healthy biological systems exhibit complex patterns of variability that can be described by mathematical chaos. This variability can be captured by sensor and are obtain under form of physiological signals. In signal processing and to describe a physiological signal, feature extraction techniques is used. A feature is a specific measurement or property extracted from a signal to represent certain relevant information or aspects of the signal. Feature extraction is an essential step that enable to the dimension reduction of signal and data compaction (Singh and Krishnan 2023). It enables to represent data with a smaller subset of feature rather

than a complete signal and to provide synthetic information for signal analysis and further processing. For example, in the case of cardiac signal, we can extract the R-peaks that corresponding to the period of ventricular contraction of the heart (**Figure 13**). It represents the electrical activation of the ventricles. The R peak is associated with the action potential of cardiac muscle cells during ventricular depolarization. It indicates the start of the systolic phase of the cardiac cycle, when the ventricles contract and expel blood into the arteries. The R-peaks is among features of cardiac signal and by which we can extract other feature such as RR intervals (**Figure 13**). In our study, we used biosensor that captured different signal kind. Each feature in each signal is more detailed in the study 4.

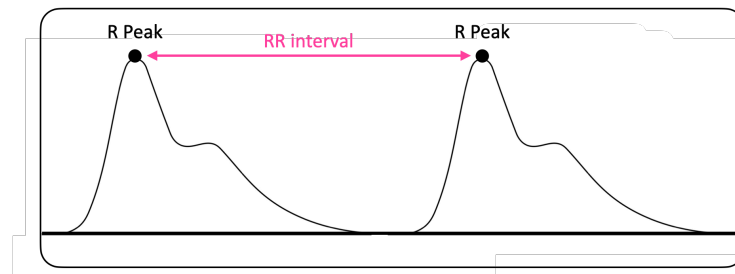


Figure 13. Example of one feature in cardiac signal.

Features are extracted by domains types that characterize different aspects of the signal: time-, frequency- or non-linear-domains:

- **Time-domain** refers to analyze of signal in context of time. Features are extracted from the raw time representation of a signal. It is calculated using time-domain analysis methods, such as mean, variance, statistical moment calculation, autocorrelation, or other similar techniques. Time-domain features provide information on the dynamic properties and temporal variations of the signal, such as trend, fluctuations, recurrent patterns or regularity. In particular, they can be used to analyze the signal's temporal structure and the relationships between signal values at different times;
- **Frequency-domain** refers to a characteristic extracted from the frequency representation of a signal. Frequency-domain features provide information on the distribution of frequencies present in the signal, such as frequency peaks, dominant

frequency bands, or energy in different frequency bands. In particular, they can be used to analyze signal variation in the frequency spectrum;

- **Non-linear-domain** features are features extracted from the analysis of a signal's non-linear properties. Unlike frequency or time domain features, which focus on the linear properties of the signal, non-linear domain features exploit the non-linear relationships and complex patterns present in the signal. These features are often based on measures derived from chaos theory, nonlinear dynamics or nonlinear time series analysis. They may include measures of complexity, irregularity, recurrence, fractality, stability or other non-linear properties of the signal. Non-linear domain features can provide additional information about the intrinsic structure and dynamics of the signal, which cannot be captured by linear features alone.

This project being exploratory, we have chosen to be exhaustive to ensure a completeness of features from data of scientific literature. A total of 190 features from all the different signals were extracted.

i. Cardiac signal

The raw signal is blood volume pulse signal (BVP). To quantify HRV from raw signal, we can extract features into 3 broad categories: frequency domain methods, time domain methods and non-linear domain methods (Ralevski, Petrakis et al. 2019):

- **Time-domain features** quantify the variability of interbeat interval measurements, (i.e., the period of time between two successive heartbeats) and provides valuable information about the changes and fluctuations in the signal over different time periods (**Figure 14**);
- **Frequency-domain features** assess the distribution of absolute or relative power across four frequency bands (heart rate (HR), ultra-low-frequency (ULF), very-low-frequency (VLF), low-frequency (LF) and high-frequency (HF)) established by The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996). The frequency domain methods are the most common and use time series analyses to evaluate HRV within different spectral components, most typically a high-frequency component (HF-HRV) that ranges

from 0.15–0.40 Hz and a low-frequency component (LF-HRV) that ranges from 0.04–0.15 Hz. Analysis of the spectral components of HRV allows to understand the modulatory effects of neural mechanisms on the sinus node (**Figure 14**);

- **Non-linear-domain features** that quantify the unpredictability of a time series and to explore nonlinear patterns and complex properties of heart rhythm (**Figure 14**).

Each feature is described below with its name, definition, formula if applicable and unit of measurement unit in study 4. As some characteristic formulas are complex, we have chosen not to write them down. In total, 65 features extracted from BVP raw data. All features extracted from NeuroKit2 package Python.

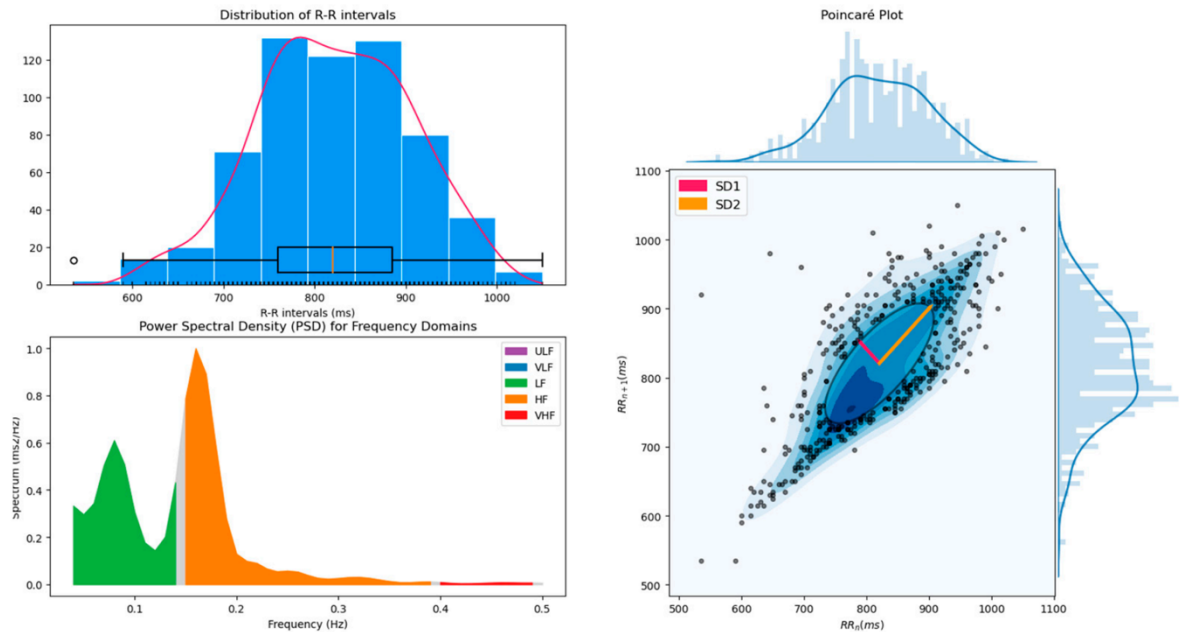


Figure 14 from (Pham, Lau et al. 2021). Example of feature extracted in different domains.

Features were extracted in time-domain (top left panel), frequency-domain (bottom left panel) and non-linear-domain (right panel).

ii. Electrodermal signal

Multiples methods for features extraction from EDA raw signal were used (Boucsein 2012) and we extracted feature from time- and frequency-domains:

- **Time-domain features** typically involve analyzing the amplitude, frequency, and duration of the skin conductance responses (SCRs). As described above, the tonic

component of EDA reflects the baseline electrical conductance of the skin and is relatively slow-changing while the phasic component represents rapid, short-duration in skin conductance. These responses (SCR) occur in response to specific stimuli, emotional events and thus, is highly sensitive to changes in SNS activity caused by emotional arousal and the orienting response to novel or significant stimuli (Boucsein 2012). Moreover, Hjorth parameters provide information on the temporal dynamics of a signal and can be used to characterize the properties of brain electrical activity or other temporal signals.

- **Frequency-domain features** provide insights into the periodic patterns and rhythmic components present in the EDA data. We have extracted frequency-domain features from EDA to convert the time-domain signal into the frequency domain using techniques like the Fast Fourier Transform (FFT). The Wavelet Transform (WT) is specifically developed to handle nonstationary signals (Cvetkovic, Übeyli et al. 2008). It accomplishes this by expressing a time function using basic, unchanging components known as wavelets. These wavelets form a family of functions derived from a central generating function called the mother wavelet through translation and dilation operations. Dilation, also referred to as scaling, either compresses or stretches the mother wavelet, while translation shifts it along the time axis. To using WT, we have to choose the appropriate wavelet and the number of decomposition levels: the WT coefficients were chosen using the Daubechies wavelet of order 4 (db4) (Cvetkovic, Übeyli et al. 2008). We have extracted feature of Mel-frequency cepstral coefficients (MFCC), a novel form of cepstrum representation built on weighted cepstrum distance measures (Shukla, Barreda-Ángeles et al. 2021). MFCC has gained widespread recognition in various pattern recognition tasks, particularly in speech signal analysis (Shukla, Barreda-Ángeles et al. 2021).

Feature of Hjorth, Wavelet and PSD have been calculated only on portion of signal (one minute with the most SCR peak). Each feature is described below with its name, definition, formula if applicable and unit of measurement unit in the study 4. In total, 109 features extracted from EDA raw data. All features extracted from Neurokit2, Pywt, scipy, numpy and librosa packages in Python.

iii. Skin temperature signal

Feature of skin temperature (TEMP) can be based on both frequency- and time-domains. Each domains provide insights into thermoregulation and physiological responses (Karthikeyan, Murugappan et al. 2012). All features and the domain of extraction are described in the study 4. Each feature was extracted from **Time-domain** that is fundamental in understanding the dynamics of skin TEMP and its relationship with various internal and external factors. This domain describes the temporal behavior of the temperature data. In total, 2 features extracted from TEMP raw data. All features extracted from Pywt, scipy and numpy packages in Python.

iv. Accelerometer signal

Features are extracted from 3-axis accelerometer raw signal. Features were extracted in different domain (Maxhuni, Muñoz-Meléndez et al. 2016). As mentioned above, the time-domain refers to analyze of signal in context of time. The fast Fourier transform (FFT) enable to switch time-domain to frequency-domain. FFT was apply on 3-axis separately and magnitude of FFT is the square sum of this 3-axis. ACC features are described in the study 4. In total, 12 features extracted from ACC raw data. All features extracted from Scipy and Numpy packages in Python.

v. Daily-life signal

Two other features concerned daily-life have been extracted because they could be impact and explain the model and are describe in the study 4.

3.4.4 Feature transformation

Features come from different physiological signals, so they don't all have the same measurement scale. This, to apply process of dimension reduction, we have to performed feature transformation. Indeed, the process of dimension reduction, as like principal analysis component (PCA) is very sensible to the scales of the variables used in the analysis. When variables have large scale differences, those with numerically larger values can dominate the analysis and strongly influence the results. This can be a problem when variables have different units of measurement or very different amplitudes of variation. For example, if one variable is measured in millimeters and another in kilograms, the variable measured in

kilograms will have a greater influence on the PCA results. Thus, we standardized the features before applying the analysis in order to place all features on the same scale and eliminate bias due to scale deviations.

To do this, we proceeded to feature transformations by testing different possibilities using data from subjects with the most important total samples (all classes combined) available. In our case, we have used data from 5 subjects with 600 total samples. This allows us to take into account all possible physiological scales according to our different classes. Different possibilities have been tested:

- **Distribution changes by transformation (6 possibilities):** refer to the modification of the original distribution. It is used to stabilize variance, reduce skewness, and make the data more normally distributed. These transformations can be valuable when dealing with data that violates the assumptions of normality or has unequal variances.
 - *Logarithm transformation (Figure 15. Graph representation of distribution changes by 6 transformations.):* This is a normalization method used to reduce scale discrepancies in data. It involves taking the logarithm of variable values. It has the advantage of reducing the amplitude of extreme values and distributing data more evenly over a logarithmic scale (Feng, Wang et al. 2014).
 - *Exponential transformation (Figure 15):* The exponential transformation consists in raising the exponential base number to the power of the transformed values.
 - *Square power transformation (Figure 15):* involves squaring each data point. It is a process of raising each value to the power of 2;
 - *Cubic power transformation (Figure 15):* This is a method that involves raising the values of a variable to the power of three (cubic). This reduces extreme values and spreads them out around the mean.
 - *Root power transformation (Figure 15):* involves taking the square root of each data point;
 - *Quadratic power transformation (Figure 15):* involves taking the square of each data point.

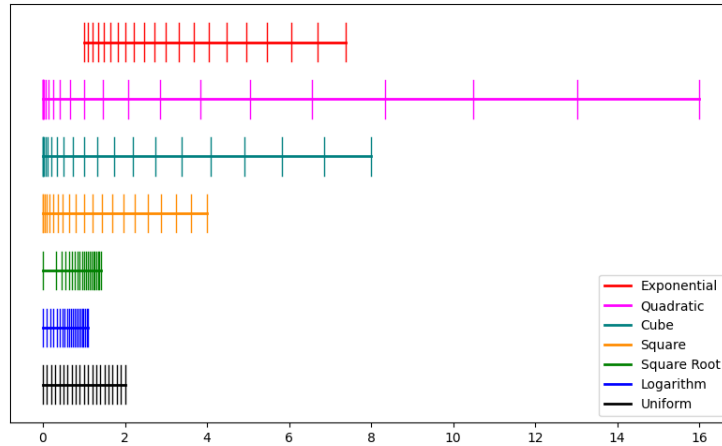


Figure 15. Graph representation of distribution changes by 6 transformations.

Transformations were exponential, quadratic, cube, square, square root or logarithm in reference to uniform scale (black in graph).

- **Robust standardization (2 possibilities):** not very sensitive to outliers. The median is subtracted (the median is a value of the variable which separates its values into two equal parts) and divided by the IQR interquartile range (IQR is a measure of dispersion obtained by making the difference between the third and first quartile) the formula is as follows (3):

$$X_{rob} = \frac{X - \text{median}}{\text{IQR}} \quad (3)$$

In all, 24 possibilities (6*2) have performed to improve and normalize features, i.e., for each feature, there are 12 transformed features. In order to obtain the most standardized features possible, we have calculated different metrics for each transformed feature: mean, standard deviation (std), quantile range (amplitude between percentiles 99% and 1%), kurtosis and skewness. **For each feature, the transformed feature the closest to 1 of SD, closest to 0 of kurtosis and skewness and closest to 0 of mean was retained for further analysis.** Thus, by this step of standardizing features, each feature will contribute equally to the analysis, regardless of its original scale. This leads to more balanced results and better representation of relationships between features.

At this step, each sample of epoch of 20 minutes belongs to a specific class (Sample labeling step), composed by a features vector (Feature extraction step) which are standardized (Feature transformation step).

3.4.5 Feature filtering

Feature filtering is a step in the feature selection process in data analysis. Its aim is to identify and eliminate features that do not contribute significantly to the performance of the model to discriminate craving period from no-craving period through physiological signals. Features were rejected in case of following criteria:

- **Missing values:** some feature has a large number of missing values or can't be calculated for epochs of 20 minutes. For example, for the frequency inferior to 0.0033Hz (occurrence every 5 minutes), it is impossible to calculate on epoch of 20 minutes.
- **Low SD (Min-Max Normalization):** features with low SD, i.e., those with little variation across dataset were filtered. To determined SD, each feature value was normalized based on the Min-Max Normalization (Salanke, Kumar et al. 2018) represented by the equation (4), which allows value of features to be scaled within a specific range [0-1]. This ensures that the SD calculated for each feature is on the same scale and comparable, while retaining maximum information on the original SD of each feature. This is done by subtracting the minimum feature value from all values, then dividing the result by the difference between the maximum and minimum features values. This ensures that all feature values lie within the specified range. Low SD threshold was of $\leq 5\%$.

$$Normalized\ score = \frac{x - \min(x)}{\max(x) - \min(x)} \quad (4)$$

Where x represents values of raw data.

- **High correlation:** If two features are highly correlated, they may provide redundant information. In this case, one of the features has been filtered to avoid redundant information. High correlation threshold was of ≥ 0.98 . The feature kept was the one with the best distribution and the closest scale to the other features.

This feature filtering step eliminates features that may be less informative and contribute less to model performance, and contributes to dimension reduction prior to any PCA and ML processes.

At this step, each sample of epoch of 20 minutes belongs to a specific class (Sample labeling step), composed by a transformed features vector (Feature extraction/transformation steps) which are filtered depending on correlation, standardized deviation and missing values (Feature filtering step).

3.4.6 *Dimension reduction*

i. Curse of dimensionality

Dimension reduction is the process of reducing the number of features in a data set, while preserving as much information as possible. The main aim of dimension reduction is to simplify data representation while maintaining important features and eliminating noise or redundancy. It overcomes the problems of the "curse of dimensionality", where a large number of variables (in our case, features) can lead to computational and modelling difficulties, as well as over-fitting problems (Poggio, Mhaskar et al. 2017). The curse of dimensionality can lead to different problems such as:

- The exponential growth of the data space as the number of dimensions increases. This means that in a high-dimensional data space, data becomes more dispersed and more evenly distributed. As a result, it becomes more difficult to find meaningful relationships or structures between data;
- Calculation and storage difficulties. Calculations become more complex and costly in terms of time and resources, as each additional dimension increases the complexity of mathematical operations. What's more, data storage also becomes a challenge, as the space required to store data increases exponentially with the number of dimensions;
- Many data analysis algorithms and techniques can encounter performance or accuracy problems when applied to high-dimensional data sets. This can lead to model overfitting, reduced prediction quality and difficulties in extracting meaningful information from the data.

To overcome this curse of dimensionality, dimension reduction is often used, with the aim of reducing the number of dimensions while retaining the most important information and eliminating redundancies. One method often used to reduce dimensionality is the Principal Component Analysis (PCA).

ii. Principal Component Analysis

PCA is a multivariate technique which the main objective is to find a more compact representation of the data by projecting the original variables (here: feature) into a new reduced-dimensional space called the "space of principal components" (Abdi and Williams 2010). The goals of PCA are to extract the most important information from original data and obtain a more compact representation of data with only most important information (Abdi and Williams 2010). PCA works by identifying the principal directions or axes that capture the maximum variance in the data. These axes, called principal components (PC), are obtained as linear combinations of the original features. PCs are ordered according to their ability to explain the total variance in the data (**Figure 16**). The first PC therefore 'capture' or 'explain' the largest part of the variance in the data, while the subsequent components capture the residual variance of lower and lower significance. Variance into data is regardless of class because PCA is a *non-supervised algorithm*, i.e., only variance into features data is analyzed, without Class Variable. To a participant being included in PCA analysis, we have choose a **threshold of 20 samples/class** to avoid overfitting (e.g., 5:1 ratio or a minimum N of 400-500) (Osborne and Costello 2004).

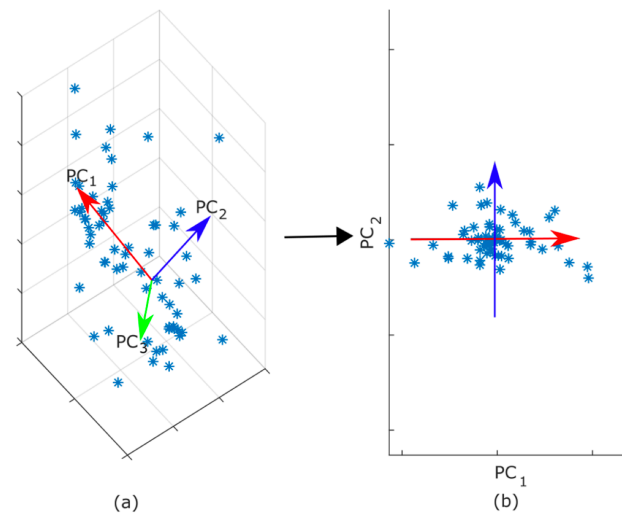


Figure 16 from (Migenda, Möller et al. 2021). Dimensionality reduction process performed with PCA.

On the left (a) Data distribution in a three-dimensional input space and the corresponding principal components; on the right (b) Projection of the data into the two-dimensional space with the PC 1, PC 2 axes.

In summarize, the PCA steps are as follows (Abdi and Williams 2010):

- PCA begins by calculating the covariance matrix from the standardized and filtered data. The covariance matrix indicates the linear relationships between the different features and is used to determine the PCs;
- By diagonalizing the covariance matrix, we obtain the eigenvectors and eigenvalues. Eigenvectors represent the directions (axes) in variable space along which the data vary most. Eigenvalues correspond to the amount of variance explained by each PC;
- PCs are ranked according to their eigenvalues, from largest to smallest. PCs with the highest eigenvalues capture a greater share of the total variance in the data;
- The percentage of variance explained by each PC is calculated by dividing the principal component's eigenvalue by the sum of all eigenvalues. This allows us to assess the relative importance of each PC in the representation of the data;
- Initial data can then be projected into the space of PCs using the eigenvectors corresponding to the selected PCs (**Figure 16**). This reduces the dimensionality of the data by replacing the original variables (features) with the new variables, the

PCs. PCs are linear combinations of features weighted by the coefficients (or weights) of the eigenvectors.

The important step of PCA is to decide how many PCs to retain in subsequent analysis. This step is able to ensure an appropriate balance between the dimensionality reduction and retaining meaningful information from the data. Many criteria can be used such as the point “elbow” of the scree plot or scree Test (the point where the eigenvalues level off or start to decrease rapidly) (Cattell 1966), the cumulative variance explained by the PCs that are around 70-80%, the Kaiser’s rule (retaining PCs with eigenvalues greater than 1) (Braeken and van Assen 2017) or the proportion of variance explained (higher proportion of variance may be given more priority). **In the case of our analysis, we have decided to take a mixed method by using all criteria.**

3.4.7 *Binary classification by Machine Learning*

The main aim being to identify physiological variations associated to craving in daily-life, the first step of model training is to classify only consistent episodes (class 0 and class 1). The second step will be to classify inconsistent classes (Class 2, 3, 4) from developed machine-learning algorithm with consistent episode.

i. Classification of consistent classes – Craving vs. No-craving episodes

The aim of this algorithm of classification is to find a hyperplane that best separates samples of different classes in a multidimensional space, i.e., the hyperplane that maximizes the margin of separation between samples of different classes. To classify our data of craving (Class 0 and Class 1), 3 classification models described below were tested:

- **Support vector machines (SVM):** works by finding the optimal hyperplane that best separates data points into different classes or predicts a continuous value. SVM aims to maximize the margin between data points of different classes to achieve better generalization;
- **Minimum distance to mean (MDM):** distance metric used for comparing the similarity or dissimilarity between two data points in a multi-dimensional space. It takes into account the correlation and covariance structure of the data, making it suitable for datasets with correlated features;

- **Linear Discriminant Analysis (LDA):** aims to maximize the distance between the means of different classes and minimize the within-class variance to enhance the separability of the classes.

To prevent overfitting, having a great reliability and an internal validity of our classifier, a technique called k-fold cross-validation was applied (we choose $k=10$) (Wong and Yeh 2020). In our dataset, 80% were used for training and 20% as a test set. This process was repeated 10 times, each time using a different subset as the test set, ensuring that each data point was tested exactly once. Then, the performance of models of test dataset have been averaged.

iii. *Classification of inconsistent classes – Classes 2, 3, 4*

These classes have not been used in this work, but will be exploited in future studies.

3.4.8 *Performance evaluation of the model classification*

The aim of these analyses is not to have the best results of classification but to optimize the pipeline of analysis process and have an indication of classification. This indication allows us to adjusting this set along the process. To have this indication, the classification was analyzed for the ability to distinguish classes with confusion matrix: craving vs. no-craving. The craving class was designated as the positive class.

In the context of a classifier, a confusion matrix of size $n \times n$ displays the predicted and true classifications, where n represents the number of different classes (Baratloo, Hosseini et al. 2015). **Table 5** illustrates a confusion matrix for the case of $n = 2$, and its entries have specific interpretations as follows:

- True negative (TN) (A in **Table 5**): is the number of correct negative predictions (specificity);
- False positive (FP) (B in **Table 5**): is the number of incorrect positive predictions;
- False negative (FN) (C in **Table 5**): is the number of incorrect negative predictions;
- True positive (TP) (D in **Table 5**): is the number of correct positive predictions (sensitivity).

Table 5. Confusion matrix for 2-class classification.

	<i>Predicted negative</i>	<i>Predicted positive</i>
<i>True negative</i>	A True Negative (TN)	B False positive (FP)
<i>True positive</i>	C False Negative (FN)	D True Positive (TP)

The confusion matrix allows to evaluated the model performance with the following standard metrics described below:

- **Sensitivity (or recall):** ability to determine positive classes (craving class) correctly (**Table 5**) (Baratloo, Hosseini et al. 2015). To estimate it, we should calculate the proportion of true positive (number of classes correctly identified as craving), describe in Equation (5):

$$Sensitivity: \frac{TP}{TP + FN} \quad (5)$$

- **Specificity:** ability to determine the negative classes (no-craving class) correctly (**Table 5**) (Baratloo, Hosseini et al. 2015), represented by Equation (6):

$$Specificity: \frac{TN}{TN + FP} \quad (6)$$

- **Precision:** the measure of the accuracy in identifying the true positive cases among all instances predicted as positive, represented by Equation (7):

$$Precision: \frac{TP}{TP + FP} \quad (7)$$

- **Accuracy:** ability of a ML model to correctly determine the classes of the data instances. It quantifies the proportion of correctly classified instances out of the total number of instances. A high accuracy indicates that the model is making a high percentage of correct predictions, while a low accuracy suggests that the

model is making a significant number of incorrect predictions. The formulate correspond to Equation (8):

$$Accuracy: \frac{TP + TN}{TP + FP + TN + FN} \quad (8)$$

- **Area under the curve (AUC) of the receiver operating characteristic (ROC) curve:**
The ROC curve is a graphical representation of the model's true positive rate (sensitivity) on the y-axis and the false positive rate (1-specificity) on the x-axis at various threshold values (from 0 to 1) (Bradley 1997, Cross and Plunkett 2014). The AUC of the ROC curve represents the area under this curve and ranges from 0 to 1. A model with an AUC of 1 indicates perfect performance, as it achieves a true positive rate of 1 (100%) and a false positive rate of 0 (0%) (Bradley 1997, Cross and Plunkett 2014). On the other hand, an AUC of 0.5 corresponds to random guessing, where the model's performance is no better than chance (**Figure 17**).

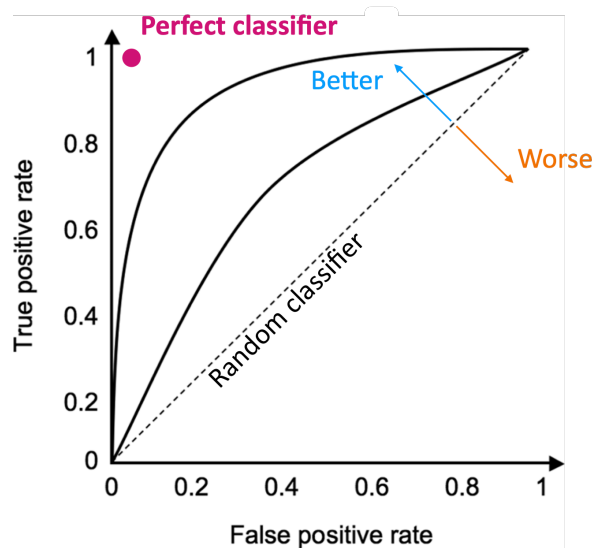


Figure 17 adapted from (Cross and Plunkett 2014). Area under the curve (AUC) of the receiver operating characteristic (ROC) curve.

3.4.9 Permutations tests

Permutation tests have been employed to evaluate the statistical significance of classifiers performance. These tests gauge the probability of achieving the observed classifier performance purely by random chance, stemming from patterns in the multi-dimensional

data that coincidentally align with the membership labels due to the limitations of a small dataset size (Ganz and Konukoglu 2017). Consequently, permutation tests provide precise regulation of error rates. To estimate statistical significance of the cross-validation classifier accuracy, we perform 100 randomized cross-validation iterations.

RESULTS

MANUSCRIPT 1:

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The centrality of craving in network analysis of five substance use disorders

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ABSTRACT

Background and aims: Among the 11 current diagnostic criteria, craving is a potential central marker for understanding and for treatment of Substance Use Disorders (SUD). Our objective was to explore craving centrality across SUD based on the study of symptom interactions in cross-sectional network analyses of DSM-5 SUD diagnostic criteria. We hypothesized the centrality of "Craving" in SUD across substance types.

Design: Participants from the ADDICTAQUI clinical cohort with regular use (2 times per week threshold for a substance) and at least one DSM-5 SUD.

Setting: Outpatient substance use treatment services in Bordeaux, France.

Participants: The sample of 1359 participants, had a mean age of 39 years old and 67% were males. The prevalence of SUD over the time course of the study was: 93% for alcohol, 98% for opioids, 94% for cocaine, 94% for cannabis and 91% tobacco.

Measurements: Construction of a Symptom Network Model conducted on the DSM-5 SUD criteria evaluated over the past 12 months for Alcohol-, Cocaine-, Tobacco-, Opioid- and Cannabis Use disorder.

Findings: The only symptom that consistently remained in terms of centrality was "Craving" [3.96 – 6.17] (z-scores), indicating that it exhibits a high degree of connections in the entire symptom network regardless of the substance.

Conclusion: Identifying craving as central in SUD symptoms network confirms the role of craving as a marker of addiction. This constitutes a major avenue in the understanding of the mechanisms of addiction, with implications to ameliorate diagnostic validity and clarify treatment targets.

1. Introduction

Substance Use Disorders (SUD) and addictive disorders may be defined as a dysregulation of control over use of rewarding substances and behaviors that translates into repeated and excessive use despite negative consequences (Auriacombe et al., 2018). Among people who use substances, those with SUD concentrate a diversity of negative health consequences such as cardiovascular diseases, cancer and accidents. Prevention of such consequences is contingent on early more accurate diagnosis and early treatment access. Currently, the diagnostic

criteria of SUD lump central criteria related to loss of control over use, and consequential criteria to excessive use (American Psychiatric Association, 2013; Auriacombe et al., 2018). There are conceptual and measurement problems with using consequences as diagnostic criteria (Martin et al., 2014). The current major diagnostic challenge for SUD and addictive disorders is to target its central or etiological criteria that should be exclusive for diagnostic purpose and are to be distinguished from its consequences that should have a value for severity assessment only.

Craving, defined as an unwanted persistent and intense desire to use

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despite negative consequences, was introduced in the DSM-5 revision of the SUD diagnostic criteria (American Psychiatric Association, 2013; Hasin et al., 2013). Daily fluctuations of craving among patients in treatment have been prospectively associated with substance use in following hours (Fatseas et al., 2015; Serre et al., 2015), and higher risk of return to problem use after use suspension in the following months or years (Cleveland et al., 2021), giving craving an etiological and prognostic value of use in addiction (Vafaei and Kober, 2022). Due to its predictive role, craving is already a treatment target for some authors (Auriacombe et al., 2018; Cavicchioli et al., 2020; Sayette, 2016; Serre et al., 2018), and is a potential central criterion for the diagnosis of SUD (Auriacombe et al., 2018; Drummond et al., 2000; Hasin et al., 2013; Hughes, 1992; Shmulewitz et al., 2021; Tiffany and Wray, 2012; Vafaei and Kober, 2022).

Latent variable methods such as item response theory (IRT), have been the preferred approach for assessing dimensional and structural validity of diagnostic criteria (Embretson and Reise, 2000). IRT analyses applied to the DSM-5 SUD criteria have shown that craving fit well with the other criteria on the underlying unidimensional latent SUD variable. Importantly, craving was the least difficult criterion and the most discriminant of all criteria when comparing across substances (Kervran et al., 2020) and samples of people with regular use (Castaldelli-Maia et al., 2018; Chung et al., 2012; Gilder et al., 2014; Shmulewitz et al., 2011, 2021). Craving appears to capture subjects with less severe SUD well, suggesting its potential utility as an early indicator of SUD (Chung et al., 2012; Kervran et al., 2020).

Recent research proposes that diagnostic criteria are dynamically directly related to each other, and that their individual analysis may provide valuable results compared to IRT method (Epskamp et al., 2017; Fried, 2015; Schlechter et al., 2021). Symptom network analysis explore the interrelationships between symptoms, considering that they are causally mutually dependent, and influence each other accordingly in these network conceptualizations (Schlechter et al., 2021). The symptom network model uses pairwise interactions among symptoms (i.e., diagnostic criteria) to represent a disorder as a web of mutually influencing symptoms (Borsboom and Cramer, 2013). This kind of model is now used in a large and diverse number of disorders (Fried, 2015; McNally et al., 2017), such as depression and anxiety (Beard et al., 2016) or post-traumatic stress disorder (McNally et al., 2014). Symptom networks based on diagnostic criteria provide an overview of the connections between symptoms. The inferences offered by such networks allow a better understanding of how disorders develop, are maintained and could be treated (Borsboom and Cramer, 2013). Especially, centrality in symptom networks could be compared across several substances to highlight the different positions occupied by each criterion in the different SUD. These positions are partially related to the distinct pharmacological and psychological properties unique to each substance and partially related to the core of loss of substance use control (disordered use) that is expected to be across the different addictions (Rhemtulla et al., 2016; Rutten et al., 2021).

Better understanding of the network structure of the SUD diagnostic criteria could be relevant to increase diagnostic accuracy. For the DSM-III-TR SUD diagnostic criteria, network analysis showed the centrality of the “Large amount” criterion (Fried et al., 2016; Rhemtulla et al., 2016) and more recently, network analysis comparing DSM-IV and DSM-5 SUD criteria showed a high centrality of the “Time spent” on substance use criteria (Rutten et al., 2021). However, in this study the DSM-5 network analyses did not include the recently added craving criterion, but only an estimate by dichotomizing the score of the abridged 5-items version of the self-administered Obsessive-Compulsive Drinking Scale (OCDS) (Rutten et al., 2021). It would be interesting to investigate the DSM-5 diagnostic criteria for SUD, with all 11 diagnostic criteria directly explored.

The main goal of this paper was to explore symptom centrality to identify which diagnostic criteria may be most important in SUD, by investigating symptom interconnectivity in cross-sectional network

analyses of DSM-5 SUD diagnostic criteria for alcohol, opioids, cocaine, cannabis and tobacco. The original hypothesis was that the craving criterion, added in the DSM-5 revision, may play a significant role in these networks regardless of the substance. Its centrality is potentially fundamental in terms of occurrence, maintenance and treatment of addiction.

2. Methods

2.1. Sample and inclusion criteria

Data were extracted from the Addiction Aquitaine cohort (ADDICTAQUI, Bordeaux, France) composed of patients seeking addiction outpatient treatment for at least one DSM-5 Use Disorder diagnosis, aged 18 years and older, who provided informed consent (Auriacombe, 2017). The cohort was approved by French Regulation and ethical committee (CNIL, CPP, CEEI/IRB). Within the framework of the DSM-5 revision process (2007–2013), the ADDICTAQUI Cohort explored the DSM-5 diagnostic criteria (Hasin et al., 2013). For larger variability in substance use severity and diagnosis, all participants included in the cohort from 2009 to 2019, and reporting regular use of a substance, were included in the network analysis of that substance. This implies that participants included in analysis for one particular substance did not necessarily have a SUD for that particular substance, but used it regularly, and had at least one diagnosis of SUD for another substance. Regular use was defined as reporting use at least 2 times per week in the past 12 months. The 11 DSM-5 SUD criteria were evaluated for the past 12 months for all participants reporting regular use of that substance. Previous research using IRT on the same sample showed the unidimensionality and psychometric validity of the 11 SUD DSM-5 diagnostic criteria (Kervran et al., 2020).

2.2. Assessments

Each participant completed a baseline interview that included a face to face standardized and structured interview conducted by trained interviewers who collected sociodemographic variables and substance use-related variables with the Addiction Severity Index (ASI) (Denis et al., 2016; McLellan et al., 1992). We adapted the MINI structured interview (Sheehan et al., 1998) to explore current (over the past 12 months) DSM-5 SUD. Presence or absence of each of the 11 DSM-5 SUD diagnostic criteria over the past 12 months were systematically explored separately for each substance associated with regular use (see details in Supplementary Materials – Table S1).

2.3. Network analysis

Network analysis is a powerful statistical approach to explore disorders as a set of interacting symptoms rather than as separate components (Epskamp et al., 2018c). Symptom networks consist of nodes (in this study: DSM-5 SUD diagnostic criteria) and edges (the connections between the symptoms/diagnostic criteria), which represent the conditional pairwise relations between two symptoms controlling for all other symptoms in the network. The methodology used in this paper (see Supplementary Materials) is related to the conventional methodology developed in the literature on psychometric analyses in symptom networks (Borsboom and Cramer, 2013), and according to the network guidelines for the computational analysis of network properties (Burger et al., 2020). Five separate analyses were performed for alcohol, opioids, cocaine, cannabis and tobacco.

First, we conducted an estimation to build the network graphical representations (Fruchterman-Reingold algorithm) of each of the five SUD, with a connection between any two diagnostic criteria (symptoms) if these diagnostic criteria were present in the same patient and with nodes depicted closer together more strongly related. We used an Ising Model (an undirected network of partial correlation coefficients for

binary data) which brings pairwise relationships (conditional dependence relations) between the diagnostic criteria and a network regularization (Epskamp et al., 2018c).

Secondly, we analyzed centrality by quantifying the structure of these five networks, at a local level, by four metrics of network analysis (Strength, Closeness, Betweenness and Expected Influence) (Bringmann et al., 2019), described in [Supplementary Materials](#). These four metrics represent the centrality. In a nutshell, centrality can be understood to reflect how connected and thus potentially clinically relevant a diagnostic criterion is in a network (via paths through other diagnostic criteria, intervening on a highly central diagnostic criterion, other nodes will be both directly and indirectly affected). Measures of centrality are given with standardized z-scores, i.e., standardized coefficients calculated by subtracting the mean and dividing by the standard deviation for each observation.

Thirdly, because sample size varied across substance classes, the resulting networks would not be comparable due to differential sparsity (e.g., in the opioid network with a sample of only $N = 131$, edges are much more easily set to 0 than in the tobacco network with $N = 1014$). To address this concern, we analyzed robustness in terms of stability of diagnostic criteria network centralities, with the calculation of the CS-coefficient.

Fourthly, the five individual SUD networks were compared to each other with a network comparison tool providing significance indices evaluating the differences between each network.

Finally, we used a modularity-based community detection algorithm (spin-glass algorithm) to detect the possible presence of two communities of diagnostic criteria in this network. These results are presented in [Supplementary Materials](#).

All analyses were performed on R (4.1.0). The details of all these computational analyses are given in [Supplementary Materials](#).

3. Results

3.1. Sample description

As described in [Table 1](#), among the 1359 individuals, mean age was 39 years old and two thirds were male (67%). The prevalence of SUD over the time course of the study, among participants reporting regular use of each substance and included in its respective network analysis was: 93% for alcohol, 98% for opioids, 94% for cocaine, 94% for cannabis and 91% tobacco. “Craving” was among the most endorsed criterion across all substances ([Table 1](#)).

3.2. Network analysis

Symptom networks of the 11 DSM-5 SUD diagnostic criteria, and topology according to their relationship are described in [Fig. 1](#) for each of the five substances (see [Fig. S1](#) for correlation matrix). No negative correlation was found.

3.3. Network inferences

Network centrality measures are described in [Fig. 2](#). “Craving” was the only diagnostic criterion that consistently remained in the most influential measures in terms of Strength, Expected Influence and Closeness (e.g., for Strength: $Alcohol=5.12$; $Cocaine=6.17$; $Tobacco=3.96$; $Opioids=5.21$; $Cannabis=4.68$ – z-scores). In addition, “Craving” criterion had consistently the highest centrality measure among these three measures, meaning that it exhibited a high degree of connections in the entire symptom network (i.e., Strength), an expected important role in the activation, persistence, and remission of the network (i.e., Expected Influence) and a shortest mean distance from other symptoms (i.e., Closeness). However, “Craving” had the highest Betweenness only for Tobacco and Cocaine, meaning that it exhibited on average the shortest path between two random diagnostic criteria of the network (i.e., Betweenness). Especially, “Withdrawal” and “Activities given-up” were the most correlated criteria with “Craving” (respectively, Pearson’s correlations for Strength: $Alcohol=0.65$; $Cocaine=0.68$; $Tobacco=0.64$; $Opioids=0.75$; $Cannabis=0.73$, and $Alcohol=0.59$; $Cocaine=0.77$; $Tobacco=0.38$; $Opioids=0.49$; $Cannabis=0.46$).

“Withdrawal” was central for Tobacco, Cannabis and Opioids only (e.g., for Strength: $Alcohol=4.60$; $Cocaine=4.78$; $Tobacco=3.55$; $Opioids=5.07$; $Cannabis=4.36$ – z-scores), although “Craving” still remained the most central of the five substances. “Activities given-up” had the second-highest centrality indices after “Craving” for Cocaine and Alcohol (e.g., for Strength: $Alcohol=5.02$; $Cocaine=5.78$; $Tobacco=3.24$; $Opioids=4.72$; $Cannabis=4.02$ – z-scores). Conversely, “Hazardous Use” was mainly excluded from the five networks in terms of centrality measures. All the other criteria had not the same centrality between the five substances. However, the criteria related to loss of control (such as “Time spent”, “Quite/control”, “Large amount” in addition to “Craving”) remained more similar between substances, and conversely, the criteria related to consequences of loss of control (such as “Tolerance”, “Withdrawal”, “Activities given-up”, “Psychological/physical problem”, “Neglect role”, “Hazardous use”, “Social/interpersonal problem”) were less similar between substances ([Fig. 2](#)).

3.4. Network robustness (stability) and modularity

In terms of stability, the network analysis appeared robust despite the frequency (variance) of the occurrences of symptoms, as shown with the bootstrap analysis, with only less stability for cocaine (see details in [Supplementary Materials – Fig. S3](#)).

3.5. Cross-substance networks

General invariance between networks compared two by two was statistically relevant as p-values were not significant for a majority of SUD, except for the centrality of Alcohol and Cannabis, and for the structure of the network for Alcohol and Tobacco ([Table 2](#)).

Table 1
Demographic and DSM-5 Diagnostic severity and endorsed criteria by participant groups with regular use ($n = 1359$).

	Total sample	Alcohol ($n = 787$)	Opioids ($n = 131$)	Cocaine ($n = 141$)	Cannabis ($n = 504$)	Tobacco ($n = 1014$)
Age – Mean (SD)	38.6 (11.5)	40.3 (11.6)	34.3 (9.7)	32.8 (7.8)	33.5 (9.6)	38.3 (11.3)
Males – n (%)	914 (67.3)	569 (72.3)	89 (67.9)	115 (81.6)	398 (79.0)	660 (65.1)
DSM-5 criteria						
No. endorsed SUD criteria – Mean (SD)	-	6.88 (3.0)	7.37 (2.6)	7.2 (3.2)	6.69 (2.9)	5.04 (2.3)
SUD – n (%)		728 (92.5)	128 (97.7)	133 (94.3)	474 (94.1)	928 (91.5)
Mild		60 (7.6)	7 (5.3)	17 (12.1)	56 (11.1)	157 (15.5)
Moderate		122 (15.5)	23 (17.6)	15 (10.6)	78 (15.4)	334 (32.9)
Severe		546 (69.4)	98 (74.8)	101 (71.6)	340 (67.5)	437 (43.1)

SD: standard deviation, SUD: Substance use disorder. Diagnosis severity SUD was defined according to the number of endorsed criteria: no diagnosis (0–1 criterion), mild (2–3 criteria), moderate (4–5 criteria) and severe (6 or more criteria) ([American Psychiatric Association, 2013](#)).

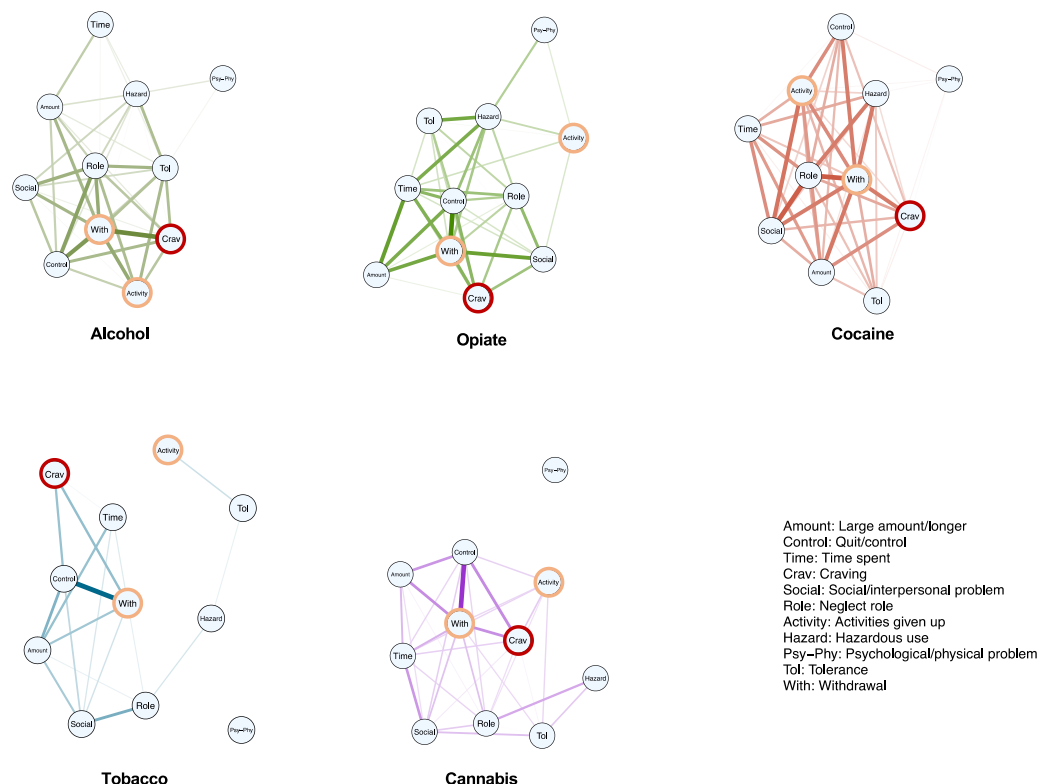


Fig. 1. Symptom network of the 11 SUD criteria for 5 substances. Symptom network describes the relationships between symptoms (diagnostic criteria) by drawing a bridge between two diagnostic criteria that are mutually present. The thickness of the lines (edges) represents the level of correlation between two symptoms. Symptoms abbreviations and their DSM-5 correspondence are defined in Table S1. The color circled nodes correspond to the three most central nodes in terms of Strength, as shown in Fig. 2. The red circle in each of the networks refers to the Craving criterion; the two orange circles refer to the Withdrawal and Activities given-up criteria.

4. Discussion

The goal of the present study was to use symptom network analysis to understand the DSM-5 SUD diagnostic criteria interactions and their centrality, across various substances (alcohol, opioids, cocaine, cannabis and tobacco), with the strong hypothesis that the craving criterion, added in the DSM-5 revision, may play a significant role in these networks regardless of the substance. To our knowledge, this study is the first network analysis of the full 11 DSM-5 SUD diagnostic criteria. We found that “Craving” was the most central diagnostic criterion across the 11 SUD criteria for the five substance networks. While considering the psychometric and conceptual limitations inherent in the use of measures of centrality in symptom networks (Hallquist et al., 2019), these results strongly suggest that craving could be a core symptom of SUD, and a fundamental target to understand and modify the network in terms of occurrence (Bringmann et al., 2019; Hallquist et al., 2019), confirming craving as a target for treatment. Comparison across substances also showed that “Craving” was particularly linked to “Activities given-up” for Alcohol and Cocaine, but not for Opioids, Cannabis or Tobacco. Conversely, “Withdrawal” was linked to the presence of “Craving” for all substances, but central only for Opioids, Cannabis and Tobacco, and not for Alcohol and Cocaine. Such results may be due to the pharmacological

properties of the different substances and the differential toxicity associated with their use (O’Brien, 2017), related to different neuro-adaptation effects consequential to use regardless of causality of use. The lack of centrality of “Withdrawal” in Alcohol and Cocaine can be interpreted through the comparison of networks. Indeed, since “Withdrawal” is peripheral in Alcohol and Cocaine, it could possibly be only the consequence of “Craving” in SUD for Opioids, Tobacco and Cannabis, and not a driving causal symptom (Auriacombe et al., 2018; Martin et al., 2014; Suzuki and Kober, 2018). These comparative interpretations should be cautious due to the lack of data on the contemporaneous and temporal connections of networks (Epskamp et al., 2018a).

Results different from ours were reported in a study comparing the DSM-IV and DSM-5 SUD criteria in a large sample of treatment attendees. In this study, “Craving” was not one of the most central criteria (Rutten et al., 2021). However, the “Craving” criterion was not assessed directly, but estimated through the score of the self-administered 5-item abbreviated version of the OCDS, that explores different subdimensions of craving over the past 7 days. This is very different from the result of an interviewer exploring the presence of the DSM-5 “Craving” criterion over the past 12 months, as done in our study. Thus, in that study, the “Craving” criterion may have been overlooked due to the short time

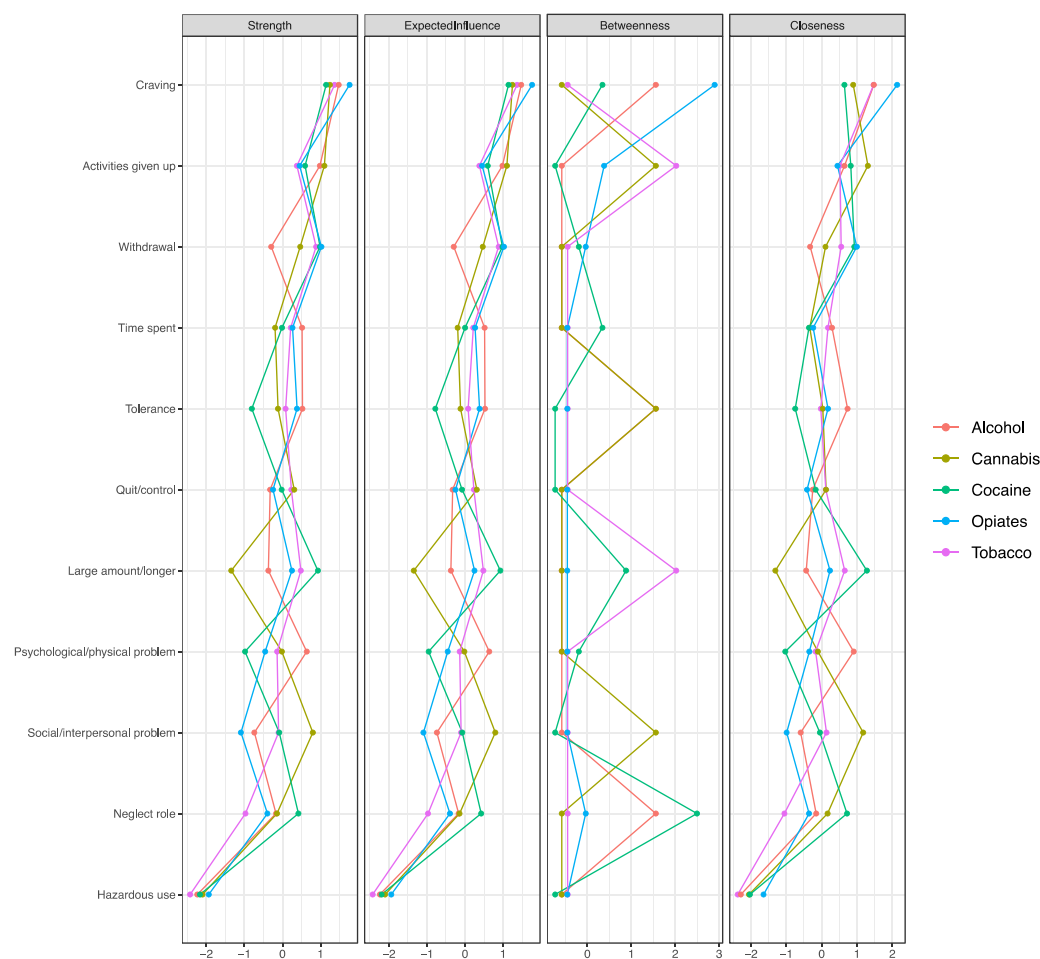


Fig. 2. The four measures of centrality (Strength, Closeness, Betweenness and Expected influence) of the 11 SUD criteria for 5 substances. In this Figure, each of the four vertical tables corresponds to a measure of centrality. Within each table, the highest centrality is on the right, the lowest is on the left. Thus, the rightmost criteria are the most central. All the tables are classified according to the decrease in centrality of the Strength (from top to bottom). The centrality number at the bottom of each vertical table, on the x-axis, shows standardized z-scores (i.e., standardized coefficients, calculated by subtracting the mean and dividing by the standard deviation for each observation). A z-score at -2 on the x-axis for Expected Influence indicates that that node has the least expected influence on the network.

frame (7 days vs. 12 months) and the use of a self-administered questionnaire instead of an interviewer exploration, especially in a population with potentially low insight and reduced ability to report symptoms (Raftery et al., 2020).

Interestingly, our results are consistent with IRT studies (Chung et al., 2012; Kervran et al., 2020; Shmulewitz et al., 2021), that demonstrated that “Craving” was the most selective of the SUD criteria across substances. Furthermore, our finding that “Hazardous Use” was a peripheral diagnostic criterion, for all the 5 substances, slightly modifying the network in its absence (Bringmann et al., 2019), is consistent with IRT studied reporting that “Hazardous Use” and “Social/interpersonal problem” due to use could be limited as indicators of the SUD construct (Shmulewitz et al., 2011). These results suggest the

possibility that this criterion could be removed in future revisions of DSM.

Comparison between networks and between substances revealed that the criteria related to loss of control (such as “Craving”, “Time spent”, “Quite/control”, “Large amount”) remained more similar between substances, and conversely, the criteria related to consequences of loss of control (such as “Tolerance”, “Withdrawal”, “Activities given-up”, “Psychological/physical problem”, “Neglect role”, “Hazardous use”, “Social/interpersonal problem”) were less similar between substances. Clinical implications of such findings are important, as currently most individuals with an addiction are screened and identified more often by the consequential criteria and treatment interventions are frequently focused on these same criteria. If our results are to be

Table 2

Network comparison tests between the five SUD networks compared two by two.

	Cannabis	Opioids	Tobacco	Cocaine	Alcohol
Cannabis	X	0.6	0.3	0.3	1
Opioids	X	X	1	1	0.3
Tobacco	X	X	X	0.9	1
Cocaine	X	X	X	X	0.2
Alcohol	X	X	X	X	X

The two numbers given in each box of the Table refer to the two measurements used in the two-by-two network comparison. At the left of each box in the Table, the network invariance ranges from 0 to 1 and refers to the difference between the absolute weighted sum scores of the network connections. In other words, it explores differences in the general structure of the network, referring to the types of the connections.

At the right of each case in the Table, the global strength invariance explores whether the overall level of connectivity is equal across networks. Overall connectivity is defined as the absolute weighted sum of all edges in the network. In other words, it explores differences in terms of centrality, referring more especially here to the strength. The result of the network comparison tests (network invariance and global strength invariance) is expressed as a p-value, which is set against an alpha level of 0.05.

confirmed, important changes in addiction clinical practice will be needed to train health professionals and the general public to more awareness about craving as a significant experience.

Symptom networks allow to distinguish central symptoms from others that are more peripheral in the network. Based on the symptom network theory, proposals for redefining disorders in psychiatry have been made (Gauld, 2022). In the context of SUD, the peripheral symptoms may be diagnostic criteria that are consequential to loss of control over use and our results raise the question of the relevance of consequences criteria in SUD diagnosis (Auriacombe et al., 2018; Martin et al., 2014). In addition to implications for addiction diagnosis, there may be implications for some of the DSM foundation (Spitzer et al., 1978). Historically, the DSM has focused on the social and personal consequences of a disorder to assess its importance and existence. Disorders are generally defined on the basis of their negative consequences for individuals and these consequences are usually the target of treatments (American Psychiatric Association, 2013). However, in other areas of medicine (i.e., cancerology or diabetology), markers in the absence of consequences are considered for diagnosis and early intervention. Our results highlight the potential role of craving in the development and persistence of addiction.

For future revisions of the DSM, a first step may be to consider craving (alone or with other central criteria as defined by DSM-5), as the central criterion (or criteria) for diagnosis – and the other criteria would be for severity measures only. Using longitudinal data, causal temporal relationships between craving and other criteria could be explored by dynamic network models to study the centrality of craving vis-à-vis the appearance of other criteria (e.g. multilevel vector autoregression (Epskamp et al., 2018b)). If future studies confirm that craving is a marker and occurs early in the development of the other criteria, it could be considered relevantly as a treatment target in the absence of other relevant criteria. Craving could in particular be the target of the suggested concept of pre-addiction (McLellan et al., 2022).

Several limitations should be acknowledged. First, analysis for a particular substance was conducted among participants with regular use of that substance (but that did not necessarily have a SUD for that substance). However, the majority of them were diagnosed with SUD for this particular substance (between 92% and 98%), and all of them had at least one diagnosis of SUD (all substances taken together) and a request for related treatment. Second, although participants with regular use have been included in this study for more variability in diagnosis and severity, the mean number of diagnostic criteria (severity) was globally high. Our sample consisted of subjects seeking outpatient treatment for an addiction and who were predominantly severe. Thus, the results cannot be generalized to all people with an addiction, especially those with less severe addiction or seeking inpatient treatment or not seeking treatment. Third, network inferences can have some inherent limitations. In particular, centrality measures may be sensitive to the frequency of onset of the disorders (Hevey, 2018). Such a measure offers the opportunity to control the impact of the number of occurrences of a

symptom on the centrality measures (Borsboom et al., 2018). Only the stability of the centrality of the Cocaine network was unsatisfactory. This lack of robustness may be related to the small number of participants in this group. Centrality inferences and cross-network comparisons with the Cocaine network should be interpreted with caution.

These network analyses revealed for the first time the centrality of the craving criterion across the different SUD, as it consistently remained in the most influential centrality measures and had a high degree of connections in the entire symptom network (i.e., network of the diagnostic criteria). These important results suggest that craving could represent a diagnostic core marker of SUD and confirms its interest as a major target for treatment across SUD. We hypothesize that this would also be the case for non-substance addictions. Indeed, some studies have confirmed the importance of craving as a criterion for some behavioral addictions (Antons et al., 2020; Hormes, 2017) and craving in non-substance addictions should be explored using symptom network analysis. The possibility of identifying a marker such as craving constitutes a major step in the better understanding of the addiction mechanisms.

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CRediT authorship contribution statement

Marc Auriacombe was the overall principal investigator, obtained funding and access to participants. Fuschia Serre and Marc Auriacombe supervised the study. Christophe Gauld, Jean-Arthur Micoulaud Franchi, Emmanuelle Baillet conceptualized and supervised the Symptom Network Analysis. Charlotte Kervran, Fuschia Serre participated in patient recruitment, data collection and database management. Christophe Gauld, Emmanuelle Baillet undertook analysis, interpretation of data and drafting of manuscript. All authors undertook the critical revision of the manuscript for important intellectual content and all authors significantly contributed to the manuscript and approved the final version.

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Conflict of interest statement

We report no conflicts of interest related to this work.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2023.109828.

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MANUSCRIPT 2:

“Is craving an early marker of SUD development and severity? A one-year longitudinal follow-up among alcohol and tobacco users not in treatment.”

Submission in progress

Is craving an early marker of SUD development and severity? A one-year longitudinal follow-up among alcohol and tobacco users not in treatment

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Conflict of interest

We report no conflicts of interest related to this work. The researchers confirm their independence from funders and sponsors.

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ABSTRACT

Context: Since its inclusion in DSM-5 SUD diagnostic criteria, craving has been shown the most prevalent and discriminant among all criteria in IRT and as a central symptom in network analysis. The aim was to study whether craving could be an early marker of addiction severity by the exploration of its influence on severity of addiction such as DSM-5 diagnostic criteria count, frequency and quantity of use.

Methods: Participants were enrolled in a prospective longitudinal 1-year follow-up study with an assessment of DSM-5 SUD diagnostic criteria, craving and use-related variables every 3 months. First, we differentiated participants according to craving endorsement (always, sometimes and never) to explore the impact of craving on DSM-5 criteria count and the frequency/quantity of use at enrollment and last follow-up. Secondly, to take account of the trajectory over one-year, we used Hierarchical linear modeling (HLM) to explore whether the presence of craving overtime was associated to a greater number of DSM-5 criteria, frequency of use and quantity of use.

Results: 85 participants were included after informed consent. 47.1% (n=40) were female with an average age of 46.3 years (SD=15.2). At enrollment, there was an association between the number of SUD criteria endorsed (excluding craving) and craving endorsement among alcohol ($p<.0001$) and tobacco users ($p<.0001$). At 12-months follow-up, the number criteria endorsed was significantly different between the three groups of craving overtime for participants who used alcohol ($p=.005$) or tobacco ($p=.001$) in sense of gradual increase (Always > Sometimes > Never craving groups). HLM showed that craving at one moment was significantly associated to an increase of criteria number and frequency of use at the same moment for alcohol ($p<.001$; $p=.002$) and tobacco ($p<.001$; $p=.025$) users, but not at the next moment.

Perspectives: Our findings suggest a dose-response association between craving and SUD criteria count, suggesting that the more time goes by, the more craving becomes entrenched, and the more this will lead to the development of other criteria. Craving could be an early marker of addiction severity and its early identification may offer opportunities to intervene before such consequences appear.

INTRODUCTION

Substance use disorders (SUDs) are the most prevalent and deadly forms of psychopathology (Steel, Marnane et al. 2014) characterized by a sustained dysregulation in the control of reinforcers that translates into persistence of use despite experience of negative consequences and the desire to modify use (American Psychiatric Association 2013, Hasin, O'Brien et al. 2013, Auriacombe, Serre et al. 2018b). Craving, defined by an unwanted and fluctuating desire to use, could be a leader of loss of control in SUD: it is both a diagnostic criterion for SUD in DSM-5 and a dynamic phenomenon that has been prospectively associated with use (Fatseas, Serre et al. 2015). Moreover, in people beginning addiction treatment its changes over the first weeks of treatment could be predictive of short- and long-term treatment outcomes (weekly, monthly, yearly) (Shiyko, Lanza et al. 2012, Cleveland, Knapp et al. 2021, Chirokoff, Abdallah et al. 2022).

Craving has occupied a central role in SUD theory and research for decades (Tiffany 1990, Skinner and Aubin 2010, Serre, Fatseas et al. 2015, Sayette 2016, Vafaie and Kober 2022) and has been added as a SUD diagnostic criterion in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) (American Psychiatric Association 2013, Hasin, O'Brien et al. 2013). Item Responses Theory (IRT) methods applied to DSM-5 SUD criteria showed that craving was the most frequently endorsed criteria and that its presence or absence was able to better differentiate individuals with the disorder from those without, across criteria, substances (Kervran, Shmulewitz et al. 2020) and different types of user samples (Shmulewitz, Keyes et al. 2011, Gilder, Gizer et al. 2014, Castaldelli-Maia, Martins et al. 2018, Kervran, Shmulewitz et al. 2021, Shmulewitz, Stohl et al. 2021). Report of craving in subjects with even mild SUD (2-3 criteria) suggests that it may be one of the first symptoms to appear or may be in itself an expression of the addictive disorder (Chung, Martin et al. 2012). Recent research on symptoms networks gives an overview of links and connections between symptoms and a better understanding on how disorders are developed, maintained and could be treated (Borsboom and Cramer 2013). Performed on the full 11 DSM-5 SUD diagnostic criteria, symptom network analysis showed the central place of craving among all criteria network (Gauld, Baillet et al. 2023). Overall, these set of research suggest that craving could be among the first symptoms to be expressed in SUD and may play a major role in its development making it a candidate marker of pre-addiction (McLellan, Koob et al. 2022).

Some longitudinal studies showed that craving or difficulty controlling use may be a prognostic indicator of future risky drinking and alcohol-related problems such as increase in the odds of binge-drinking (Morgenstern, DiFranza et al. 2016). More recently, in a one-year prospective study among users of cannabis with problems, craving was the most endorsed criterion among the DSM-5 loss-of-control criteria (use longer than planned, failing to quit or control use despite the desire to do so) (Fink, Shmulewitz et al. 2022). Research on tobacco addiction in adolescents showed that craving can appear within days to weeks after the onset of occasional use, and could constitute the first self-reported symptoms of SUD (DiFranza, Rigotti et al. 2000, Gervais, O'Loughlin et al. 2006), suggesting that they could be part of the SUD core criteria and constitute etiological symptoms of the disease. One longitudinal study, investigated the development of alcohol use disorder (AUD) with 1- and 3-years follow-ups with DSM-IV criteria and ICD-10 craving criterion and showed that craving was able to predict the course of AUD with other loss-of-control criteria (de Bruijn, van den Brink et al. 2005). Yet, to our knowledge, no studies have explored specifically the emergence of craving on SUD development and severity with DSM-5 diagnostic criteria among adult substance users not in treatment and not requesting access to treatment. For a better prevention of SUD development, it could be especially important to understand whether craving overtime is predictive of SUD development and severity across different SUDs.

The purpose of this study was to evaluate if craving was an early symptom of SUD and a marker of severity in a sample of substance users self-selected that are not in treatment or attempting to access treatment. In this perspective, we first explored the endorsement of the DSM-5 SUD criteria (except craving criterion) at one-year and at each time of follow-up to determine if the presence of craving at baseline, its persistence over time was associated with more severity (symptom count) and more use (quantity/frequency). We hypothesized that the presence of craving would be prospectively associated with greater severity and more use over the 12-month observation.

METHODS

Sample and procedures

Between June 2021 and July 2022, participants were recruited by way of Kanopee, a smartphone application available to the general population to screen for experiences of

problems with addictive substances (Auriacombe, Fournet et al. 2021). To be eligible for study enrollment, participants had to be adults (>18 years), current users of tobacco and/or alcohol, and not in addiction treatment. Kanopee users meeting these criteria were informed by a notification on their phone that they were eligible. They could then send their contact details to be included in the study by phone. Non-inclusion criteria were not being reachable by phone, to present a physical, psychiatric or cognitive disorder preventing data collection or difficulties in French language. After online informed consent, participants were enrolled in a prospective longitudinal 1-year follow-up study with an assessment every 3 months. Assessments were conducted by phone at baseline, 3-months (3M), 6-months (6M), 9-months (9M) and 12-months (12M) follow-up. To compensate for time, participants received 10€ for each completed follow-up. The study was approved by French Clinical Research Regulations and Data Management Agency (authorization n° ID RCB: 2021-A01220-41, MR003).

Measures of Substance Use, Craving and DSM-5 SUD symptoms

The 11 individual **DSM-5 SUD diagnostic criteria** were assessed over the past 12 months at baseline (T0) and over the past 3 months at each follow-up with the Mini International Neuropsychiatric Interview (MINI) adapted for DSM-5 criteria (Sheehan, Lecrubier et al. 1998). The **use-related variables**, such as number of use days and quantity of use in the past 30 days, were assessed using the “Substances” section of the Addiction Severity Index (McLellan, Kushner et al. 1992). We used the French validated version of the ASI adapted for tobacco and behavioral addictions (Denis, Fatséas et al. 2016). The frequency of use and quantity of use (alcohol unit (A.U.) or cigarette number) were assessed in the past 30 days of each interview (baseline and follow-ups). Also, from the ASI we collected information about being cared for by an addiction health professional lifetime and past 12-months at baseline and in the last 3-months at follow-ups.

Statistical analysis

Participants were compared on sociodemographic (e.g., age, gender, education...) and SUD characteristics (e.g., DSM-5 SUD diagnosis, frequency and intensity of craving in the past 30 days, ASI severity...) according to each substance type for which there was use (alcohol or tobacco). Participants were assigned to the alcohol group if they used alcohol in the last 12-months; and they were assigned to the tobacco group if they used tobacco in the last 12-

months. Some participants were assigned to both groups. A comparison of socio-demographic characteristics and use behavior between participants included in a single group or participants included in both groups was carried out.

Firstly, to test our hypothesis which was to explore whether craving could be an early symptom of SUD severity, we explored the influence of reporting craving at inclusion (presence or absence) on the number of criteria, other than craving, at the end of study (12-months (12M) follow-up) controlling for status of the number of criteria at T0. Then, to take account of the variability of craving overtime on the number of SUD criteria at 12M, we classified participants according to the presence or absence of craving (never, always, sometimes):

- Always Craving Group (C_{Always}) if endorsed at all available assessments (0M, 3M, 6M, 9M, 12M);
- Never Craving Group (C_{Never}) if never endorsed at all available assessments;
- Sometimes Craving Group ($C_{Sometimes}$) if endorsed sometimes.

The number of endorsed criteria (except craving criterion) and quantities used (number of day and quantities per day) were compared with Kruskal-Wallis test between each group. Post-hoc analyses for multiple comparisons were done between each group with a Dunn's rank-sum test.

Secondly, we tested the direction of a potential association between craving and the number of criteria and the frequency/quantity of use by taking into account each craving assessment and the nested nature of the data. For this, we used hierarchical linear and non-linear modeling (HLM) (Raudenbush, Bryk et al. 2005) that involved within-person variance for craving, substance use and the number of criteria as well as between-person variance for clinical and sociodemographic characteristics. To test our hypothesis which was to explore whether craving could be an early symptom of SUD severity, we examined (1) whether craving at T0 was associated with more criteria, frequency of use and quantity of use at the same assessment and (2) whether craving at T0 was associated with more criteria, frequency of use and quantity of use at the next assessment. For (1), a random coefficient regression model tested the influence of craving at T0 on the number of criteria at T0; and for (2) a random

coefficient regression model tested the influence of craving at T0 on the number of criteria at T1 (controlling for status of the dependent variable at T0), then the cross-level interaction of time was tested on this association. The number of criteria and the frequency/quantity of use were time-lagged for prospective associations. The variable of criteria number excluded craving. Each model was performed separately between alcohol and tobacco samples. The alcohol group allowed us to carry out these analyses on criteria and frequency of use (*Criteria*: Cohen D=0.8 corresponding to large effect size ($>.80$) and Adjusted intraclass correlation coefficient [ICC]=0.74 corresponding to large ICC ($p=.50$); *Frequency of use*: Cohen D=.81 and adjusted ICC=0.70) but not on quantity of use due to small effect size (D Cohen=0.17 and adjusted ICC=0.74) (Arend and Schäfer 2019). The Tobacco group allowed us to carry out these analysis on criteria and frequency of use (*Criteria*: Cohen D=1.33 and adjusted ICC=0.66; *Frequency of use*: Cohen D=0.90 and adjusted ICC=0.88)) but not on quantity of use (Cohen D=0.55 and adjusted ICC=0.84) (Arend and Schäfer 2019). Consequently, this second part of analysis were conducted only for the number of criteria and the frequency of use for both substance groups. Missing data were handled by excluding that particular observation from analyses. Continuous variables were group-centered (i.e., centered around the individual's own mean) for within-person variables, and grand-centered (around the sample average) for between-person variables.

An alpha level of .05 was used in all analyses. All analyzes were performed on JMP Pro (15.0) and on R Studio (4.1.0) with package lme4. Codes are available upon request from the first author.

RESULTS

Sample description

Among the 210 Kanopee app users who were informed by notification on their phone of the possibility to participate in the study, 160 (76.7%) sent their contact details to be included and of these, 85 (53.1%) individuals were included. Thus, 40.5% of those who were notified were included. These 85 participants were included after informed consent, 47.1% (n=40) were woman, with an average age of 46.3 years ([SD]=15.2). They were included for use of alcohol (n=84, 98.8% of the total sample,) and/or of tobacco (n=42, 68.8% of the total sample). 38 individuals were included in both groups and they were not significantly different

compared to individuals included only in one group on gender ($p=.655$), on severity for alcohol use disorder (AUD) ($p=.059$) or tobacco use disorder (TUD) ($p=.089$), but they were younger ($p=.014$). At baseline, among alcohol users, 48.8% ($n=41$) met criteria for life time SUD for 9.1 years ($SD=12.6$) and 33.3% reported craving for alcohol with a mean frequency of 1.5 days in the past 30 days ($SD=4.8$) and a mean intensity of 5.6 ($SD=2.0$). Among tobacco users at baseline, they were 95.2% ($n=40$) to meet criteria for lifetime SUD for 22.1 years ($SD=13.5$) and the majority (88.1%) reported craving for tobacco with a mean frequency of 15.4 days in the past 30 days ($SD=13.4$) and mean intensity of 7.3 ($SD=1.8$). 48.8% of participants among the alcohol sample met criteria for SUD at inclusion, and 95.2 % among the tobacco sample. All groups combined follow-up retention at 3M, 6M, 9M and 12M was respectively 85%, 75%, 68% and 79%. During the course of the study, 6 participants (7%) initiated addiction treatment.

[TABLE 1]

Number of DSM-5 criteria, frequency and quantity used at 12-months follow-up by presence of craving at inclusion and by craving groups overtime: alcohol group

At inclusion ($n=84$) there was an association on the number of AUD criteria endorsed (excluding craving) between those reporting craving ($\bar{X}=3.32$ criteria, $SD=2.31$) versus not reporting craving ($\bar{X}=0.94$, $SD=1.29$) (Linear regression: $E=.46$; $SE=.08$; $T\text{-ratio}=5.33$; $p<.0001$) but this association was not significant at 12-months follow-up (Linear regression: $E=-.07$; $SE=.17$; $T\text{-ratio}=-.40$; $p=.693$) (craving at t_0 : $\bar{X}=2.45$ criteria ($SD=1.74$) vs. No craving at t_0 : $\bar{X}=0.67$ ($SD=1.14$)) (Figure 1A). **Over the 12-months study period ($n=75$)**, 6% ($n=4$) of participants were in the Always craving group (C_{Always}), 52% ($n=39$) in the Never craving group (C_{Never}) and 42% ($n=32$) in the Sometimes craving group (C_{Sometime}). The number of AUD criteria (excluding craving) endorsed was significantly different between the three groups (Kruskal-Wallis: $\chi^2=10.41$, $dof=2$, $p=.005$) (Figure 2). The number of criteria was greater in C_{Always} with a mean of 2.33 ($SD=2.31$), then C_{Sometime} with a mean of 1.46 ($SD=1.70$) and finally C_{Never} with a mean of 0.50 ($SD=0.84$) (Figure 2A). Post-hoc analysis showed significant differences between C_{Always} vs. C_{Never} groups (Dunn rank-sum: $Z=-2.27$, $p=0.023$) and C_{Sometime} vs. C_{Never} groups (Dunn rank-sum: $Z=2.6$, $p=.005$). The difference found between C_{Always} vs. C_{Sometime} groups was not significant (Dunn rank-sum: $Z=0.89$, $p=.374$). The number of use days was significantly different between the three groups (Kruskal-Wallis: $\chi^2=13.15$, $dof=2$, $p=.002$). The

number of use days was greater in C_{Always} with a mean of 9.75 days ($SD=3.29$), then $C_{Sometime}$ with a mean of 9.59 ($SD=7.27$) and finally C_{Never} with a mean of 4.92 ($SD=1.02$) (Figure 2B). Post-hoc analysis showed a significant difference between C_{Always} vs. C_{Never} groups (Dunn rank-sum: $Z=2.26$, $p=.024$) and $C_{Sometime}$ vs. C_{Never} groups (Dunn rank-sum: $Z=3.24$, $p=.001$). However, the difference was not significant between C_{Always} vs. $C_{Sometime}$ groups (Dunn rank-sum: $Z=0.48$, $p=.630$). The quantity of use reported between the three groups of craving was not significant (Kruskal-Wallis: $\chi^2=3.67$, $dof=2$, $p=.159$) with a mean of 4.50 A.U. ($SD=4.3$) in C_{Always} , 2.97 ($SD=2.10$) in $C_{Sometime}$ and 2.12 ($SD=1.09$) in C_{Never} (Figure 2C).

[FIGURE 1]

Effect of craving status at one-moment (cross-sectional) and overtime (prospective) on the number of criteria and frequency used: alcohol group

The HLM model estimating the influence of the craving status at one-moment or over time on the number of AUD criteria and the frequency of use among alcohol users are presented in Table 2. Concerning the cross-sectional analysis, the average number of criteria was 1.05 when there was no craving ($E=1.05$; $SE=.16$; $T\text{-ratio}=6.70$; $p<.001$). When there was craving, there was on average an increase of 1.25 criteria. This cross-sectional effect was significant ($E=1.25$; $SE=.15$; $T\text{-ratio}=8.05$; $p<.001$) and was also found for the frequency of use ($E=2.32$; $SE=.75$; $T\text{-ratio}=3.08$; $p=0.002$). Concerning the prospective analysis, there was no effect of craving at T0 on the number of criteria at T1 ($E=.18$; $SE=.19$; $T\text{-ratio}=.95$; $p=.341$), but there was a significant effect of the number of criteria at T0 ($E=.81$; $SE=.06$; $T\text{-ratio}=14.12$; $p<.001$) indicating that the number of criteria at T0 predicted an increase of number of criteria at T1. There was an effect of time ($E=-.05$; $SE=.02$; $T\text{-ratio}=-2.67$; $p<.001$) in the sense of a decrease of the number of AUD criteria overtime. Moreover, craving at T0 had a significant effect on the frequency of use at T1 ($E=1.96$; $SE=0.88$; $T\text{-ratio}=2.23$; $p=.027$) indicating that the presence of craving with an increase of 1.06 days in frequency of use. The frequency of use at T0 had also a significant effect on the frequency of use at T1 ($E=0.66$; $SE=0.05$; $T\text{-ratio}=13.33$; $p<0.001$) but there was no effect of the interaction of time and craving at t0 ($E=-.28$; $SE=.26$; $T\text{-ratio}=-1.10$; $p=.273$).

[TABLE 2]

Number of DSM-5 criteria, frequency and quantity used at 12-months follow-up by presence of craving at inclusion and by craving groups overtime: tobacco group

At inclusion (n=42) there was an association on the number of TUD criteria endorsed (excluding craving) between those reporting craving (\bar{X} =4.66 criteria, SD=2.02) versus not reporting craving (\bar{X} =2.33, SD=1.09) (Linear regression: E =.68; SE =.17; T -ratio=4.07; p <.0001) but this association was not significant at 12-months follow-up (Linear regression: E =-.41; SE =.57; T -ratio=-.72; p =.479) (craving at t0: \bar{X} =3.56 (SD=2.45) vs. No craving at t0: \bar{X} =1.00 (SD=1.38)) (Figure 1B). **Over the 12-months study duration (n=39)**, 54% (n=22) of participants were in the Always craving group (C_{Always}), 8% (n=3) in the Never craving group (C_{Never}) and 38% (n=15) in the Sometimes craving group ($C_{Sometime}$). The number of TUD criteria (excluding craving) endorsed was significantly different between the three groups (Kruskall-Wallis: χ^2 =13.84, dof = 2, p =.001) (Figure 3). The number of criteria was greater in C_{Always} with a mean of 4.35 (SD=2.31), then $C_{Sometime}$ with a mean of 1.6 (SD=1.50) and finally C_{Never} with a mean of 1.00 (SD=1.41). Post-hoc analysis showed significant differences between C_{Always} vs. $C_{Sometime}$ groups (Dunn rank-sum: Z =3.42, p =.002), but was not significant between $C_{Sometime}$ vs. C_{Never} groups (Dunn rank-sum: Z =0.41, p =1.0) and between C_{Always} vs. C_{Never} groups (Dunn rank-sum: Z =1.97, p =.146) (Figure 3A). The average number of use days in C_{Always} was 20.6 days (SD=13.3), 10.7 (SD=14.0) in $C_{Sometime}$ and 4.00 (SD=5.3) in C_{Never} (Figure 3B) and was not significant between the three groups (Kruskal-Wallis: χ^2 =3.95, dof = 2, p =.138). Results about the quantity of use was not significant between the three groups (Kruskal-Wallis: χ^2 =5.28, dof = 2, p =.071) (Figure 3C). The mean quantity of use was of 10.43 cigarettes (SD=8.67) in C_{Always} , 5.36 (SD=5.39) in $C_{Sometime}$ and 7.5 (SD=0.71) in C_{Never} .

[FIGURE 2]

Effect of craving status at one-moment (cross-sectional) and overtime (prospective) on the number of criteria and frequency used: tobacco group

The HLM model estimating the influence of craving status at one-moment or over time on the number of TUD criteria and the frequency of use among tobacco users are presented in Table 2. Concerning the cross-sectional analysis, the average number of criteria was 2.42 when there was no craving (E =2.42; SE =.40; T -ratio=5.98; p <.001). When there was craving,

there was on average an increase of 1.27 criteria. This cross-sectional effect was significant ($E=1.27$; $SE=.37$; $T\text{-ratio}=3.44$; $p<.001$) and was also found for the frequency of use ($E=4.37$; $SE=1.93$; $T\text{-ratio}=2.27$; $p=.025$). Concerning the prospective analysis, there was no effect of craving at T0 on the number of criteria at T1 ($E=.68$; $SE=.39$; $T\text{-ratio}=1.75$; $p=.084$), but there was a significant effect of the number of criteria at T0 ($E=.68$; $SE=.07$; $T\text{-ratio}=9.81$; $p<.001$) indicating that the number of criteria at T0 predicted an increase of the number of criteria at T1. There was an effect of time ($E=-.14$; $SE=.04$; $T\text{-ratio}=-3.48$; $p<.001$) in the sense of a decrease of the number of TUD criteria overtime. The effect of craving at T0 on the frequency of use at T1 was not significant ($E=2.40$; $SE=1.85$; $T\text{-ratio}=1.30$; $p=.198$). But, the frequency of use at T0 had a significant effect on the frequency of use at T1 ($E=0.78$; $SE=0.05$; $T\text{-ratio}=14.07$; $p<0.001$) but there was no effect of time ($E=-.33$; $SE=.21$; $T\text{-ratio}=-1.54$; $p=0.127$).

[TABLE 3]

DISCUSSION

The purpose of this 12-month follow-up study was to determine whether craving could be an early symptom of addiction severity. To this end, we recruited from the general population individuals with a regular use of alcohol or/and tobacco, not in treatment, and not attempting to access treatment. We hypothesized that the presence of craving at one time and over the 12-month period would be associated quantitatively to greater severity (number of diagnostic criteria, number of days use and quantities used per day). To our knowledges, this study is the first to explore whether, in a general population-based sample, craving at one-moment and overtime is predictive of SUD development and severity for alcohol and tobacco users. To study the influence of craving as a potential early symptom of SUD, we explored craving status at inclusion (presence or absence), then over time by its endorsement frequency (Always, Sometimes, Never) and looked at the association with DSM-5 symptom count (excluding craving) and quantity/frequency of use at 12-months follow-up. At baseline, the number of SUD criteria endorsed was significantly different according to craving status at baseline but this was not found at 12 months. These results suggest that craving could be a differentiating marker of SUD severity or development but that overall, our samples were too severe at baseline to observe the early value of craving. Moreover, by analyzing craving over time, and not just its presence at the time of inclusion, our results show that participants,

whether alcohol or tobacco users, that always reported craving had greater severity compared to those that never reported craving, and that those that reported craving sometimes were in-between for severity. These results were also found for frequency of use among alcohol users, but not among tobacco users. These results suggest a dose-dependent response relationship between “dose” of craving, (always, sometimes, never) and severity and use days “response” (number of SUD symptoms and number of days use). Whether alcohol, or tobacco group, quantities used on days of use, were not associated to craving status. To explore the direction of the association, while taking into account the within- and between-person variability of craving overtime (at each point of the longitudinal study), we used hierarchical linear modeling. Our results showed that craving at one-moment lead to develop more severity (criteria count and frequency of use) at the same moment and at the next-moment for the frequency of use for alcohol group, around 3-months later, but this was not significant for criteria count at the next moment.

Taken together, these finding suggests that the presence of craving maybe a prognostic marker of the development of a greater number of SUD criteria and use days over time. In other words, craving alone could act as a warning signal that could predict (and thus be a target for prevention), the development or worsening of SUD. This study underlines and brings new results in regard to recent findings of IRT and network studies which demonstrated that craving was the most selective and central of all DSM-5 SUD criteria across substances (Shmulewitz, Keyes et al. 2011, Gilder, Gizer et al. 2014, Castaldelli-Maia, Martins et al. 2018, Kervran, Shmulewitz et al. 2020, Kervran, Shmulewitz et al. 2021, Shmulewitz, Stohl et al. 2021, Gauld, Baillet et al. 2023). But these studies used cross-sectional data (Wang and Cheng 2020), while our study used a time-series to collect craving at regular intervals (every 3 months) over one-year. Our study monitored both the influence of craving at the same assessment and changes over a one-year time period to establish causal relationships by using HLM. Although our study does not report a prospective link between craving at one point and the number of criteria at the next assessment, we do find this link between craving and use, and a cross-sectional link between craving and both the number of criteria and use. Several studies have reported a positive association between an increase in craving at a given time, and an increase in the likelihood of reporting substance use in the following hours, supporting that craving is a trigger for use in daily life across substances both in human lab and daily life

settings (Serre, Fatseas et al. 2015, Panlilio, Stull et al. 2019, Cavicchioli, Vassena et al. 2020, Burgess-Hull, Panlilio et al. 2022, Ellis, Mun et al. 2022, Vafaie and Kober 2022). This study provides a new element in this regard confirming that craving is a trigger for use even 3-months later. Furthermore, our findings suggest that the more time goes by, the more craving becomes entrenched, and the more this will lead to the development of other criteria with a dose-responses effect, which is in line with our hypothesis that craving could be one of the first symptoms of addiction to appear. Indeed, we suggest that craving could acts as a driver symptom leading to the development of SUD, notably through continued use of reinforcing substances. Our suggestion is reinforced by recent research suggesting that craving may play a causative role in use and relapse (Vafaie and Kober 2022). Furthermore, recently a fMRI neuromarker, was able to discriminate substance users (with SUD and/or heavy users) from non-users based on response to substance and food cues (Koban, Wager et al. 2023). Currently most individuals with an addiction are screened and identified more often by the consequential criteria, and treatment interventions are frequently focused on these same criteria. Our results suggests that craving may be among the first symptoms to appear in SUD severity development and that exploration of this symptom in the general population could allow to access individuals before the occurrence of the consequences criteria, thus reducing the burden of addiction.

Important limitations have to be acknowledged. The first limitation is the time window of our longitudinal study that could be too short, or too late, for exploration of the development of SUD. However, other longitudinal studies, investigated the development of SUD with 1- and 3-years follow-ups suggesting that the duration of 12-months period might be adapted, although craving criterion that was not studied (de Bruijn, van den Brink et al. 2005). The longitudinal design of our study does provide some information about relationships. Yet, due to the limited sample size, results have to be taken with precaution and generalizability of results to other samples should be investigated, including larger samples with other addictive substances or behaviors. In particular, in future investigations, it would be interesting to study the sometimes craving group in greater detail, to explore the different craving states and there outcome on severity. The advantage of our study was to recruit participants not in treatment or not requesting access to treatment at the beginning of the study to avoid the influence of treatment interventions. The recruitment was via KANOPEE

app that is an app developed to screen for problem substance use (Auriacombe, Fournet et al. 2021). Even if participants were not in treatment at inclusion, they represented a population concerned about their use, which could constitute a bias by targeting only a part of the general population concerned with identifying possible addiction problems. In this regard, although this number was small, some participants-initiated treatment for an addiction during the study. However, not all participant of our sample had SUD. Severity levels mainly ranged from mild to moderate (average from 2.1 criteria for alcohol to 5.1 for tobacco) and only 11% and 48% with respectively severe AUD and TUD composed our sample, giving us access overall to a population less severe than those receiving SUD treatment (70% and 43% respectively) (Kervran, Shmulewitz et al. 2020, Gauld, Baillet et al. 2023). Furthermore, although many people contacted us to take part in the study (n=160), only 53.1% (n=85) were actually included, the others being unreachable by phone or email. Another limitation concerned participants who were recruited in both the tobacco and alcohol groups. This phenomenon is common, studies identified tobacco and alcohol as substances used commonly together (Merikangas and McClair 2012). Participants included in both the tobacco and alcohol group were not significantly different about severity of addiction or gender but they were younger in line with study which found that that being younger were associated with risk to having multiple SUDs (John, Zhu et al. 2018). Diagnostic criteria for alcohol and tobacco use disorders were assessed independently for inclusion purpose. Finally, the phenomenon of response dose-dependent was regardless of substance type that is consistent with literature suggesting that craving occupies a central place in addiction across substances (Kervran, Shmulewitz et al. 2020, Vafaie and Kober 2022, Gauld, Baillet et al. 2023), and influences use and relapse across addiction types (Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2015, Serre, Fatseas et al. 2018, Vafaie and Kober 2022).

CONCLUSION

The use of substances with reinforcing effects is widespread, and morbidity and mortality associated with their use, especially alcohol and tobacco, is well documented by numerous epidemiological studies (Degenhardt, Charlson et al. 2018). Within populations who use these substances, some will eventually meet criteria for addiction, which stands as the most prevalent and financially burdensome psychiatric disorder (Steel, Marnane et al. 2014). The transition from substance use to SUD is uncommon, and when it does happen, this

progression is often neither linear nor rapid allowing both a window of time for prevention and intervention, but also for more marked use leading to greater health consequences. Recently, the *preaddiction* concept has been introduced to describe the stage in which substance use begins to transition to SUD (McLellan, Koob et al. 2022). In this preaddiction framework, this study suggests that craving might to be an early and predictive marker of SUD development and could constitute a screening target in early-stage SUD. Early identification of people who are more at risk for SUD development may offer opportunities to intervene before such consequences appear and craving and its early assessment may contribute to both detection and prevention of SUDs.

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Table 1. Description of samples

N=85	Alcohol users (N=84)		Tobacco users (N=42)	
	% (n)	\bar{X} (SD)	% (n)	\bar{X} (SD)
Gender (woman)	46.4 (39)		57.1 (24)	
Age		46.1 (15.3)		42.3 (14.3)
Employed (executive job)	31.3 (26)		21.9 (9)	
Married	67.6 (48)		63.6 (21)	
Education		15.4 (2.5)		14.8 (2.4)
Follow-up number				
Year of regular use		9.1 (12.6)		22.1 (13.5)
Day of use in the past 30 days		9.5 (7.9)		21.3 (12.4)
ASI severity (0 – 9)		1.6 (1.4)		4.1 (2.3)
MINI severity (0 – 11)		2.1 (2.32)		5.1 (2.3)
DSM-5 SUD endorsement	48.8 (41)		95.2 (40)	
Mild	25.0 (21)		23.8 (10)	
Moderate	13.1 (11)		23.8 (10)	
Severe	10.7 (9)		47.6 (20)	

Table 2. Cross-level interaction of craving variability at t0 and t+1 on the number of criteria (except craving) and the frequency of use at t0 and t+1 among alcohol and tobacco groups

Outcomes	Predictors	Alcohol group*				Tobacco group**			
			SE	T-ratio	p-value		SE	T-ratio	p-value
Criteria T0	Intercept	1.05	0.16	6.70	<0.001	2.42	0.40	5.98	<0.001
Criteria T0	Craving T0	1.25	0.15	8.05	<0.001 ^A	1.27	0.37	3.44	<0.001 ^A
Use frequency T0	Intercept	7.91	0.72	11.01	<0.001	14.63	2.36	6.19	<0.001
Use frequency T0	Craving T0	2.32	0.75	3.08	0.002 ^A	4.37	1.93	2.27	0.025 ^A
Criteria T1	Intercept	0.35	0.09	3.98	<0.001	0.78	0.32	2.46	0.016
Criteria T1	Craving T0	0.18	0.19	0.95	0.341	0.68	0.39	1.75	0.084
Criteria T1	Criteria T0	0.81	0.06	14.12	<0.001 ^A	0.68	0.07	9.81	<0.001 ^A
Criteria T1	Time	-0.05	0.02	-2.67	0.009 ^A	-0.14	0.04	-3.48	<0.001 ^A
Use frequency T1	Intercept	2.79	0.55	5.08	<0.001	3.28	1.72	1.91	0.059
Use frequency T1	Craving T0	1.96	0.88	2.23	0.027 ^B	2.40	1.85	1.30	0.198
Use frequency T1	Use frequency T0	0.66	0.05	13.33	<0.001 ^A	0.78	0.05	14.07	<0.001 ^A
Use frequency T1	Time	-0.11	0.10	-1.11	0.267	-0.33	0.21	-1.54	0.127
Use frequency T1	Craving T0*Time	-0.28	0.26	-1.10	0.273				

* N participants = 84; N assessments = 5; N observations = 309

** N participants = 39; N assessments = 5; N observations = 160

^A Surviving correction for age, gender and addiction treatment

^B Surviving correction for age and addiction treatment but not gender

Figure 1. Number average of criteria endorsed at inclusion (0M) and at 12-months follow-up (12M) by presence of craving at inclusion. A) Among alcohol users; B) Among tobacco users.

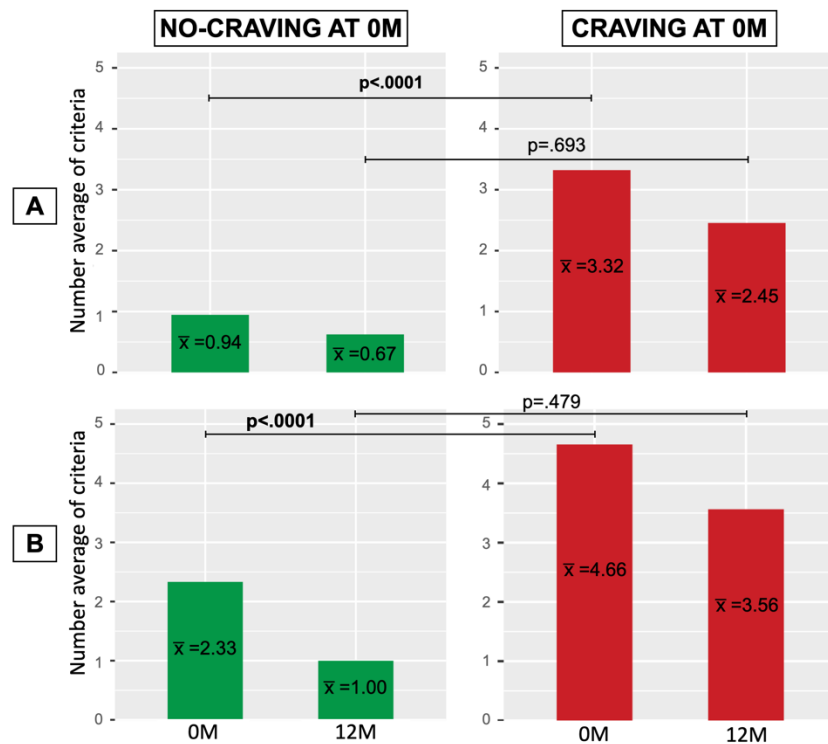


Figure 2. Number of criteria endorsed, frequency of use days and quantity of use between craving groups among participants who use regularly alcohol. (A) Number of endorsed DSM-5 SUD criteria at 12-months follow-up except craving criterion; (B) Number of use days in the last 30 days at 12-months follow-up; and (C) Quantity of use in the last 30 days at 12-months follow-up.

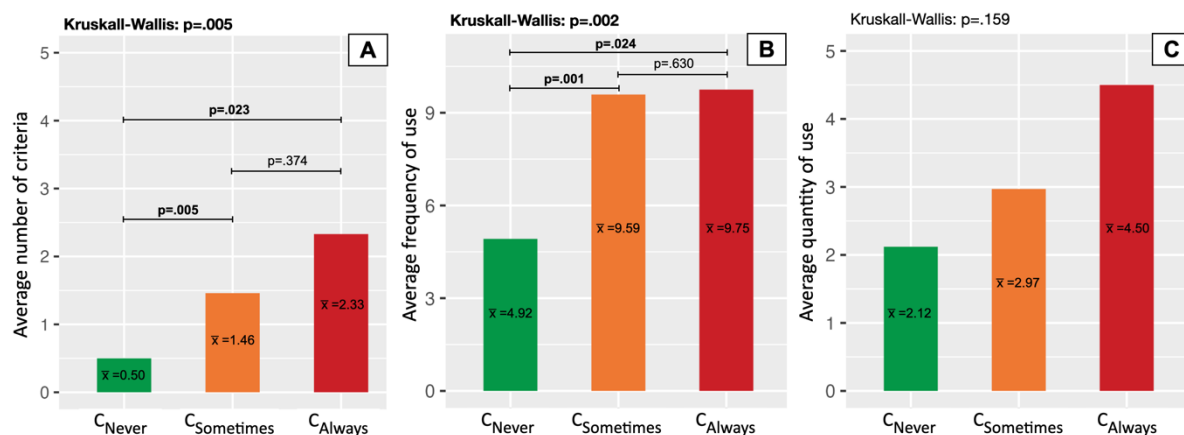
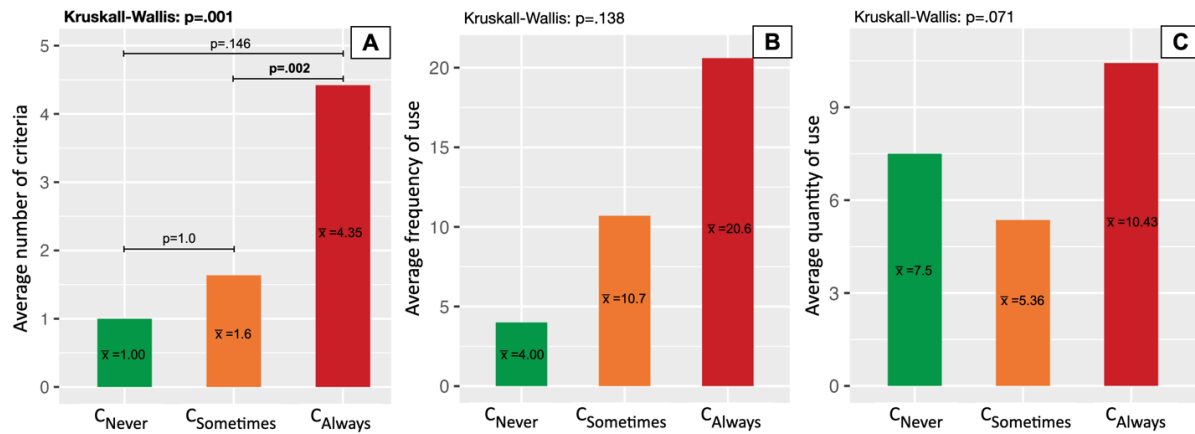


Figure 3. Number of criteria endorsed, frequency of use days and quantity of use between craving groups among participants who use regularly tobacco. (A) Number of endorsed DSM-5 SUD criteria at 12-months follow-up except craving criterion; (B) Number of use days in the last 30 days at 12-months follow-up; and (C) Quantity of use in the last 30 days at 12-months follow-up.



MANUSCRIPT 3:

“Craving changes in first 14 days of addiction treatment as a predictor of 5 years relapse status”

Submission in progress

Craving changes in first 14 days of addiction treatment as a predictor of 5 years relapse status

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Running head: "Craving: predictor of long-term relapse"

ABSTRACT

Addiction is considered a chronic disorder that requires long-term treatment. Daily fluctuations of craving have been shown to predict substance use and relapse within hours, making it a transdiagnostic target for treatment across substances. Early identification of predictors of long-term outcomes may enable better and early adjustment of treatment. The objective of this study was to examine whether trajectory and temporal dynamics of craving at the beginning of addiction treatment were associated to long-term outcome. An Ecological Momentary Assessment study collected craving and substance use during the first 14-days of treatment, followed by prospective regular follow-ups for 5 years or more to assess long-term outcomes. 39 participants beginning addiction treatment for different substances were recruited in an outpatient clinic. Analysis investigated whether individual differences in craving trajectory and dynamics at treatment initiation predicted 5 years or more follow-up outcome: *relapse* versus *remission*. The results showed that *relapse* status at 5+ years was significantly associated with a slower decrease of craving intensity ($p=.013$), and a lower craving inertia ($p=.038$), during the beginning of treatment, compared to *remission* status. However, craving intensity at the beginning of treatment was not found associated with relapse/remission status at 5+ years follow-up. Results suggest that a slower decrease in craving at treatment initiation could express a greater resistance to treatment long term. This resistance may have many mechanisms, among which a greater reactivity to cues (as suggested by lower inertia), that could constitute a persistent vulnerability to relapse, and a valuable indicator of long-term outcomes.

INTRODUCTION

Substance Use Disorders (SUD) are characterized by a loss of or reduced control of substance use, and persistence of use despite its negative consequences (American Psychiatric Association 2013, Hasin, O'Brien et al. 2013, Auriacombe, Serre et al. 2018). SUD, such as alcohol, tobacco, cannabis or opiate use disorders, are chronic disorders characterized by frequent relapses despite efforts to cut-down or abstain from substance use (Witkiewitz and Marlatt 2007). The objective of SUD treatment is to achieve stable abstinence or a significant reduction of use through the reduction of relapse frequency over time (Auriacombe, Serre et al. 2018). On average, people achieve stable abstinence after several treatment episodes, and long-duration treatment episodes are preferable to repeated but shorter episodes (Dennis, Scott et al. 2005, Brandon, Vidrine et al. 2007, Dennis and Scott 2007). To that end, it could be interesting to examine whether early treatment response could be a marker of long-term treatment outcome (5 years or more). Getting information about future treatment outcome could allow for better early adjustment of treatment.

The outcomes of SUD treatments may be influenced by different factors, including so-called “distal” and “proximal” factors (Witkiewitz and Marlatt 2004). Distal factors include characteristics of individuals and/or their environment (McKay, Franklin et al. 2006), levels of motivation and self-efficacy (Hopkins, Spears et al. 2022), meaningfulness (Knapp, Brick et al. 2021), psychiatric comorbidities (Weinstock, Alessi et al. 2007, Calabria, Degenhardt et al. 2010), or SUD severity (Tiet, Ilgen et al. 2007). These distal factors could make the individual more vulnerable to relapse, or to more proximal triggers such as craving (Moore, Seavey et al. 2014, Serre, Fatseas et al. 2018) or stress (Sinha 2001). Craving, defined as an unwanted persistent and intense desire to use despite knowledge of negative consequences, is considered as an important potential proximal trigger of relapse across all addictions (Serre, Fatseas et al. 2015, Auriacombe, Serre et al. 2018, Serre, Fatseas et al. 2018, Cavicchioli, Vassena et al. 2020, Vafaie and Kober 2022), and has occupied a central role in SUD theory and research for decades (Tiffany 1990, Skinner and Aubin 2010, Sayette 2016). It has been added as a SUD diagnostic criterion in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) (American Psychiatric Association 2013, Hasin, O'Brien et al. 2013, Auriacombe, Serre et al. 2018), and has been demonstrated to be central in network of SUD criteria (Gauld, Baillet et al. 2023) and the most prevalent and discriminant from all SUD

criteria when comparing across substances (Kervran, Shmulewitz et al. 2020) and between different types of user samples (Shmulewitz, Keyes et al. 2011, Gilder, Gizer et al. 2014, Castaldelli-Maia, Martins et al. 2018, Kervran, Shmulewitz et al. 2021, Shmulewitz, Stohl et al. 2021). Craving is currently considered by many authors as a transdiagnostic and major treatment target to reduce relapse frequency (O'Brien 2005 a, Auriacombe, Serre et al. 2018), regardless of substance type (Vafaie and Kober 2022, Koban, Wager et al. 2023).

Craving occurrence and intensity can vary rapidly over the course of a day. People frequently describe strong fluctuations in craving with peaks (Drummond, Litten et al. 2000, Tiffany, Warthen et al. 2009). Studies assessing craving using retrospective measures have the disadvantage of memory bias, such as lumping of episodes, or on the contrary, selecting some episodes and not others. Moreover, some individuals may have limited insight of their substance-seeking behaviors, reducing the ability to retrospectively recall and report past experiences (Nisbett and Wilson 1977). These barriers can be overcome by using daily life monitoring, such as Ecological Momentary Assessment (EMA), to allow real time measurement of individual momentary states, with the help of mobile technology, in the natural environment and in real time, through repeated measurements over time limiting memory bias (Stone and Shiffman 1994, Wrzus and Neubauer 2023). This method enables the examination of within-person fluctuations in individual experiences, their temporal relationships, and considers the influence of the environment. EMA has been adapted and validated for the study of craving in SUD (Serre, Fatseas et al. 2012), and such studies have revealed within-person and within-day variability of craving (Bujarski, Roche et al. 2015, Cleveland, Knapp et al. 2021). Several EMA studies reported a positive association between an increase in craving at a given time, and an increase in the likelihood of reporting substance use in the following hours, confirming that craving is an important proximal trigger for relapse in daily life across substances (Serre, Fatseas et al. 2015, Panlilio, Stull et al. 2019, Cavicchioli, Vassena et al. 2020, Burgess-Hull, Panlilio et al. 2022, Ellis, Mun et al. 2022). A recent metaanalysis including both EMA and non-EMA studies concluded on a strong prospective relationship of self-reported craving with future substance use / relapse, even for medium term intervals (over 1 year) (Vafaie and Kober 2022).

Beyond measuring averaged intensity at any given moment that does not account for the influence of time, recent literature in psychology and psychiatry has shown the importance to take into account the dynamic variability of symptoms or risk factors over time (Ebner-Priemer, Eid et al. 2009). Some indices can be used to characterize dynamic fluctuations, such as the *inertia*, *variability* or *instability*. *Inertia* (or temporal dependency) refers to the autocorrelation (AR1) between consecutive measures (Trull, Lane et al. 2015). A high inertia reflects a tendency to persist from one moment to the other, and can reflect lower sensitivity in response to fluctuations in environmental demand, or less reactivity to substance cues (conditional stimuli associated in past experiences of substance use and that can trigger a conditioned response, regardless of presence of the addictive substance). *Variability*, calculated by within-person Standard Deviation (SD), reflects the overall amplitude of changes. *Instability*, calculated by the Mean Square Successive Differences (MSSD) index, can be defined as the magnitude of symptom changes from one moment to the next (Lamers, Swendsen et al. 2018). The instability is conceptualized as the combination of variability and inertia. These metrics have been used in EMA studies to capture dynamic processes of mood disorders (Lamers, Swendsen et al. 2018, Johns, Di et al. 2019, Panaite, Rottenberg et al. 2020), obsessive-compulsive disorders (Landmann, Cludius et al. 2019), their impact on treatment response (Husen, Rafaeli et al. 2016) and more recently, substance use disorders (Chirokoff, Abdallah et al. 2022, Ellis, Mun et al. 2022).

EMA studies investigating the dynamic fluctuations of craving at the beginning of treatment reported generally an increase of craving intensity on quit day (McCarthy, Piasecki et al. 2006, Bujarski, Roche et al. 2015), followed by a decrease during the first few weeks after cessation (Shiyko, Lanza et al. 2012, Cleveland, Knapp et al. 2021). Interestingly, one study observed a faster decrease of tobacco craving at the beginning of treatment in individuals who remained abstinent within the first month, compared to those who relapsed (Shiyko, Lanza et al. 2012). Another EMA study reported that participants who relapsed in the 4 months following treatment discharge, presented lower craving variability during the inpatient treatment (Cleveland, Knapp et al. 2021). Thus, early changes in craving at treatment initiation appear to be informative about short-term treatment responses. However, it remains to be explored whether these changes of craving at treatment initiation may represent a potential predictor of longer-term outcomes. Indeed, identifying early

indicators of disorder progression would enable to adjust treatment intensity and duration accordingly, to better prevent relapse and increase treatment effectiveness, as for many other chronic diseases (Konerman, Yapali et al. 2014, Lai, Dimko et al. 2015, Greenberg, Jacobson et al. 2022). Furthermore, this is the opportunity to investigate craving's role in the mechanism of addiction by examining how much craving change in response to an intervention has long term impact which would further promote craving as a proximal marker of addiction.

The objective of this study was to examine whether dynamic fluctuations of craving, (including craving dynamic parameters), in daily life, during the initial 14-days of SUD outpatient treatment, was associated with relapse/remission outcome at 5 years and more. We hypothesized that a more rapid decrease of craving at the beginning of treatment would be predictive of a higher probability of remission at 5 years or more.

SUBJECTS AND METHODS

Study design and sample

Analyses were conducted on data from a sample of participants in a 14-day EMA study, and then followed-up within the ADDICTAQUI cohort. Participants were subjects between 18 and 65 years of age (to avoid the bias of possible age-related cognitive impairments), starting treatment for a DSM-5 alcohol, tobacco, cannabis, or opiate use disorder (of at least moderate severity) in an outpatient addiction treatment clinic in Bordeaux, France. The participants received standard comprehensive care, consisting of individual behavioral treatment focused on relapse prevention and psychosocial support, combined when available with pharmacotherapy. After establishing a target quit date according to the patient's personal goals, full abstinence was encouraged as an outcome, with no negative consequences for the patient if this goal was not met. They were free from active psychosis or severe cognitive impairment and provided informed consent for participation in research. Both studies (ADDICTAQUI cohort and EMA study) were approved by French biomedical research regulations and ethical committees (EMA study: CPP SOOM III/DC-2009/01 CNIL/DR-2015-408; ADDICTAQUI Cohort: CPPPRB BORDEAUX/B01-20 CNIL/997082).

ADDICTAQUI cohort procedure (Auriacombe 2019)

Participants beginning outpatient treatment for addiction (SUD or behavioral addiction) received a clinical interview to assess addiction severity and psychiatric comorbidities. Diagnoses of current psychiatric disorders, including SUD, were assessed using the Mini International Neuropsychiatric Interview–Plus (MINI) (Sheehan, Lecrubier et al. 1998), adapted for DSM-5 criteria. Number of endorsed SUD criteria defined *MINI addiction severity (from 0 to 11)*. Substance-use characteristics and multi-dimensional addiction severity were assessed using a validated French version of the Addiction Severity Index (ASI) (McLellan, Kushner et al. 1992), modified to take into account tobacco addiction (McLellan, Kushner et al. 1992, Denis, Fatséas et al. 2016). The ASI is a standardized interview conducted by trained interviewers who collected sociodemographic variables and substance use-related variables. When multiple SUD co-occurred, the *primary substance* was determined according to the main problematic substance reported by the individual, and on which the treatment was focused. The Interviewer Severity Ratings (ISR) from the drug/alcohol/tobacco section of the ASI were used to assess the *ASI addiction severity (from 0 to 9)*. According to ADDICTAQUI Cohort procedure, participants were re-assessed with ASI every 6 months after inclusion in the study, regardless of their status in treatment (follow-up interviews).

EMA study procedure

From May 2009 to July 2013, ADDICTAQUI participants who started treatment for an alcohol, tobacco, cannabis, or opiate use disorder of at least moderate severity, and free from active psychosis or severe cognitive impairment, were offered to participate in an EMA study. This protocol was previously described in detail (Serre, Fatseas et al. 2012). EMA assessments started after a target-quit date jointly determined by the participant and his addiction physician. Following a training session, each participant received a personal digital assistant (PDA) to carry for 14 days. Each PDA was programmed to administer four electronic surveys per day, between 8:00 am and 11:00 pm, inquiring about primary substance use and craving (see below). The signal schedule was also chosen for participants to accommodate their usual sleep schedule. Signal times were fixed for each individual but randomized across participants in the sample using 20 distinct signaling programs. At the end of study, a debriefing appointment was held to ask a few questions about use, craving and the medications used during the study, as well as to return the material and arrange compensation. Financial

compensation was provided as a function of number of electronic surveys completed, with a maximum of 100 euros for participants who completed 75% or more of the electronic assessments.

Measures

Craving and use

At each electronic survey of EMA study, participants were asked to rate the maximum level of craving (i.e., the desire to use the primary substance) that they felt since the previous assessment on a 7-point scale (from 1 no desire to 7 extreme desire, single-item). They were also asked if they had used this primary substance since the previous assessment, followed by questions concerning the use of any other psychoactive substances during that time period.

Relapse/Remission status at 5+ years follow-up

Primary substance use was collected at follow-up assessments (ADDICTAQUI Cohort) with the ASI. Relapse was defined as non-abstinence, i.e.: at least 1 day of use of the primary substance in the past 30 days. Participants were classified into 2 categories according to the status of their primary substance use: *relapse* or *remission*.

Analyses strategy

In the EMA study, due to a restricted number of assessments occurring on the starting and ending day of the study, and their overlap with investigator contact, only data collected between days 2 and 13 were analyzed.

To test our hypotheses, we explored the association between craving trajectory and dynamics during the first 14 days of treatment (captured with the EMA study), and relapse outcome status at 5+ years follow-up (captured with ADDICTAQUI Cohort follow-ups). Hierarchical linear and nonlinear modeling (Raudenbush, Bryk et al. 2005) was used to account for the multilevel structure of the data that involved within-person variance for craving and substance use, as well as between-person variance for clinical and sociodemographic characteristics.

Prior to model estimation, participants were compared according to relapse outcome status at 5+ years follow-up on initial characteristics and severity. Then, craving intensity variability during the EMA study was explored by intraclass correlation (ICC), and a value of 0.56 indicated that 44% of variance accounted for within-person variability. Then, variability of craving was assessed at 3 different levels: the person level (*level 3*), the day level (*level 2*) and the assessment level (*level 1*) (Cleveland, Knapp et al. 2021). For this, a *three-level unconditional model* was estimated (see in Supplementary Materials – Method S1 & Table S1). The average craving across all persons, days and assessments was 3.44, on a scale from 1 to 7, as shown by the fixed effects parameter. Regarding the variability of craving, it seems that the craving variance was greatest at the person-level, with a variance of 2.48 (SD=1.57) than at the day level with a variance of 0.31 (SD=0.56) and at the assessment level with a variance of 1.75 (SD=1.32), and this is why craving dynamic parameters were estimated at the person-level. Further HLM analysis only considered assessment- and person-levels.

To examine the first hypothesis that relapse/remission status at 5+ years is associated with differences in time-dependent evolution (trajectory) of craving at the beginning of treatment, first a random coefficient regression model tested the influence of time (day in study) on craving intensity. Then the cross-level interaction of relapse status was tested on this association (see Supplementary Materials – Method S2).

To explore if relapse status was associated with differences in craving dynamics at the beginning of treatment, the inertia, variability, and instability metrics of craving were calculated at the person-level (as this was the level with the greatest variability, compared to the variability observed at the day level and the assessment level). The craving *inertia* was obtained by means of average within-person autocorrelation (AR1) of craving at time t and craving at time $t-1$, the craving *variability* by the within-person Standard Deviation (SD), and the craving *instability* by the within-person root mean square of successive differences (rMSSD) (Neuman 1941, Jahng, Wood et al. 2008). Associations between relapse status and each craving metrics were tested with logistic regression, while controlling the within-person average craving intensity.

Additional analyses were conducted to explore if relapse status was associated with difference in EMA reports of craving intensity, substance use (primary substance, and other substance uses) and in the craving-use relationship at beginning of treatment. For this, prospective associations between craving at one time, and primary substance use at the next assessment were explored. These time-lagged analyses examined within-day (and not across-day) associations. Then, relapse status was added as an interaction term.

In all HLM analyses, continuous variables were group-centered (i.e., centered around the individual's own mean) for within-person variables, and grand-centered (around the sample average) for between-person variables. Concerning missing data (NA) (20.1% of EMA data), Kendall's τ_b tests were conducted to evaluate whether NA were missing completely at random (MCAR), missing at random (MAR) or not missing at random (NMAR) (Pugh, Brown et al. 2022). No correlation was found between craving NA and day on study ($Z=1.106$, $\tau=.08$, $p=.095$), assessment number ($Z= -1.472$, $\tau=-.03$, $p=-.141$), primary substance use ($Z=1.393$, $\tau=.04$, $p=.164$), other substance uses ($Z=.817$, $\tau=.02$, $p=.414$), suggesting that missing data on craving were MCAR/MAR. Thus, NA were handled by excluding that particular observation from analyses.

Analyses were performed in the entire sample, independently of the primary substance. Influence of sex, age, medication, and substance type (introduced as dummy variables) was tested individually on the main outcomes in each model (craving intensity, substance use, influence of day on craving, influence of craving on substance use) and if significant, the factor was added to the final model.

An alpha level of .05 was used in all analyses.

Data analysis

All analyzes were performed on JMP Pro (15.0), R (4.1.0) and HLM (8.0).

RESULTS

Sample description

Among the 159 participants who were included both in ADDICTAQUI Cohort and EMA study, only those with an available follow-up assessment at 5 years or more were selected. When several follow-ups were available after 5 years, the latest was considered for this study. This sample (N=39) was compared with participants with no follow-up available at 5 years or more (N=120), and they were not significantly different, on baseline socio-demographic characteristics (age: $p=.621$, sex: $p=.767$), or on ASI addiction severity ($p=.562$). Nonetheless, they differed on primary substance, and were more frequently in the alcohol group and less frequently in the opiates group ($p=.047$) compared to the 120 subjects not included in this analysis.

Table 1 describes the clinical characteristics of the sample. The average long-term follow-up time was 6.5 years ($SD=12.7$) after treatment initiation, and 51% ($n=20$) of participants reported at least one day of primary substance use in the past 30 days, and were considered as the relapse group. Relapse status was not significantly associated with age (Wilcoxon: $Z=.21$; $\chi^2=.05$, $p=.822$), sex ($p=1.0$), medication ($p=.232$) or substance type ($p=.201$). At inclusion, the relapse group and the remission group were not significantly different on ASI addiction severity (6.5 vs. 6.5 respectively, Wilcoxon: $Z=0.16$; $\chi^2=.03$, $p=.854$), or DSM-5 SUD severity based on MINI (6.1 vs. 6.0, Wilcoxon: $Z=-0.13$; $\chi^2=.02$, $p=.885$) and number of days of use in past 30 days (25.2 vs. 25.3, Wilcoxon: $Z=-0.53$; $\chi^2=.31$, $p=.581$). On the contrary, at follow-up, relapse group ASI addiction severity was significantly higher compared to remission group (3.4 versus 0.9 respectively, Wilcoxon: $Z=-4.04$; $\chi^2=16.47$, $p<.0001$), they reported an average of 16.6 days of use, and a majority of them (70%, $n=14$) had regular use (more than 8 times in the last month) (and 0 days for the remission group) ($SD= 12.5$; Min-Max=1-30; median= 15.5) (Wilcoxon: $Z=-5.69$; $\chi^2=32.57$, $p<.0001$).

Response rate to the 14-days-EMA surveys was 79.9% ($n=1497$). Among the 1497 assessments completed, craving episodes (non-null intensity) and primary substance use were reported respectively in 67% and 34% of assessments (Table 2).

[TABLE 2]

Craving trajectory during first 14 days and association with relapse status at 5+ years

Craving intensity reported in the first 14-days of treatment was not influenced by age ($\gamma=.01$; $SE=.02$; $df=36$; $T\text{-ratio}=.643$; $p=.524$), sex ($\gamma=-.11$; $SE=.52$; $df=36$; $T\text{-ratio}=-.219$; $p=.828$) or medication ($\gamma=-.36$; $SE=.04$; $df=36$; $T\text{-ratio}=-.563$; $p=.577$). Craving intensity was higher in cannabis ($\gamma=1.47$; $SE=.58$; $df=34$; $T\text{-ratio}=2.52$; $p=.016$) and opiate groups ($\gamma=1.43$; $SE=.70$; $df=34$; $T\text{-ratio}=2.04$; $p=.049$), but not in tobacco group ($\gamma=.44$; $SE=.62$; $df=34$; $T\text{-ratio}=.71$; $p=.482$), when compared to alcohol group (see Supplementary Materials – Results S3). Relapse status was not found associated with the craving intensity while controlling on substance type ($\gamma=-1.14$; $SE=.49$; $df=33$; $T\text{-ratio}=-.288$; $p=.775$) (Table 2).

Overall, increasing time in the first 14 days of treatment was significantly associated with a decrease in craving intensity ($\gamma=-.05$; $SE=.02$; $df=38$; $T\text{-ratio}=-2.60$; $p=.013$), and this effect was not significantly modified by age ($\gamma=-.01$; $SE=.002$; $df=35$; $T\text{-ratio}=-.032$; $p=.974$), sex ($\gamma=-.01$; $SE=.04$; $df=35$; $T\text{-ratio}=-.77$; $p=.448$), medication ($\gamma=.05$; $SE=.04$; $df=36$; $T\text{-ratio}=1.08$; $p=.287$) or substance type: tobacco ($\gamma=-.02$; $SE=.06$; $df=34$; $T\text{-ratio}=-.324$; $p=.748$), opiate ($\gamma=.04$; $SE=.11$; $df=34$; $T\text{-ratio}=-.369$; $p=.715$) or cannabis ($\gamma=-.05$; $SE=.05$; $df=34$; $T\text{-ratio}=-1.04$; $p=.305$) with the alcohol group as reference.

Relapse status at 5+ years, when added as an interaction term in the model testing the influence of days on craving intensity, was significant ($\gamma=.08$; $SE=.04$; $df=37$; $T\text{-ratio}=2.10$; $p=.043$) (Table 3), indicating a slower decrease for participants in the relapse group (Figure 1).

[TABLE 3]

[FIGURE 1]

Craving dynamic parameters and association with relapse at follow-up

Craving dynamic parameters of inertia, variability and instability estimated at the person-level were presented in Figure 2. These parameters were not influenced by age ($p=.074$, $p=.985$ and $p=.303$ respectively), sex ($p=.166$, $p=.831$ and $p=.704$ respectively), medication ($p=.230$,

p=.430 and p=.299 respectively) or by substance type (p=.179, p=.835 and p=.764 respectively) (see Supplementary Materials – Results S3).

Comparisons between relapse and remission groups at follow-up were inconclusive for craving instability ($\beta=-.15$; SE=.41; $\chi^2=.13$; p=.720) and for craving variability ($\beta=-.66$; SE=.60; $\chi^2=1.23$; p=.256). By contrast, a significant difference ($\beta=-2.78$; SE=1.42; $\chi^2=3.83$; p=.034) was observed for craving inertia, in the direction of low inertia in the relapse group (Figure 2).

[FIGURE 2]

Association of relapse status at 5+ years with craving, use, and the craving-use association at beginning of treatment

Primary substance use reported in the first 14-days of treatment was not found significantly influenced by sex ($\gamma=-.96$; SE=.51; df=36; T-ratio=-1.882; p=.068), medication ($\gamma=.85$; SE=.75; df=36; T-ratio=1.137; p=.263) or by substance type (tobacco ($\gamma=.74$; SE=.632; df=34; T-ratio=1.174; p=.249), cannabis ($\gamma=.06$; SE=.60; df=34; T-ratio=.103; p=.918), opiate ($\gamma=-.90$; SE=.46; df=34; T-ratio=-1.958; p=.058) with alcohol group as reference). However, primary substance use increased with age ($\gamma=.05$; SE=.02; df=36; T-ratio=2.49; p=.018). Relapse status at follow-up was not found associated with primary substance use, while controlling on age ($\gamma=.091$; SE=.453; df=35; T-ratio=.200 p=.843).

Prospective analysis revealed that an increase in craving intensity reported at a given time was significantly associated with a greater likelihood of reporting primary substance use at the next assessment approximately four hours later ($\gamma=.15$; SE=.04; df=38; T-ratio=3.11; p=.004). This prospective association was not found significantly influenced by age ($\gamma=.01$; SE=.02; df=35; T-ratio=.615; p=.543), sex ($\gamma=-.07$; SE=.53; df=35; T-ratio=-.144; p=.887) or medication ($\gamma=.16$; SE=.115; df=36; T-ratio=1.380; p=.176). However, a stronger association was observed for craving and substance use in patients in the alcohol group relative to tobacco ($\gamma=-.31$; SE=.094; df=34; T-ratio=-3.261; p=.003), opiate ($\gamma=-.814$; SE=.09; df=34; T-ratio=-8.949; p<.001) or cannabis ($\gamma=-.35$; SE=.13; df=34; T-ratio=-2.691; p=.011) groups. The influence of craving on later substance use was not significantly modified by relapse status

when added as an interaction term ($\gamma = -.01$; $SE = .09$; $df = 33$; $T\text{-ratio} = -.129$; $p = .898$) while controlling on substance type.

DISCUSSION

Across all substance addictions, craving is an important precipitant of use and relapse within hours (Serre, Fatseas et al. 2015, Vafaie and Kober 2022), but few studies have examined the impact of early craving changes over the first days of treatment on long-term outcome (several years). The current study assessed craving and its fluctuations in daily life at the beginning of outpatient treatment for SUD, and long-term treatment relapse/remission outcome. The aim was to examine whether craving trajectory and dynamics (inertia, variability, instability) during 14 days at treatment initiation could be associated with 5+ years outcome. We hypothesized that a stronger decrease in craving at initiation of treatment (i.e.: a better treatment response) would be associated with a higher probability for remission at follow-up.

Craving intensity demonstrated an overall decrease during the first two-weeks of treatment, but this decrease was slower for participants classified in the relapse group at 5+ years follow-up. Similar results were previously reported for one-month abstinence in patients treated for tobacco use disorder (Shiyko, Lanza et al. 2012). Other studies also reported that trajectories of craving or withdrawal after cessation appeared to be highly predictive of subsequent relapse (Piasecki, Jorenby et al. 2003, McCarthy, Piasecki et al. 2006, Piper, Federmen et al. 2008, Piper, Schlam et al. 2011). But these findings were only reported for short-term outcomes (one year or less). Our study is the first to demonstrate that craving trajectory during the first two-weeks of treatment, captured in daily-life by EMA, could be predictive of long-term outcome after 5 years or more. Exploration of craving dynamics brings interesting elements to understand craving and its association with outcome and hints towards possible mechanisms. In this study, craving instability and variability at inclusion were not found significantly different between the relapse and the remission groups at 5+ years. On the contrary, a lower craving inertia was observed in the relapse group while controlling for average intensity of craving. Inertia quantifies changes from one moment to the next, and high inertia reflects resistance to change i.e., persistence of states. Thus, this result suggests that, for participants who will be in the relapse group at 5 years or more, craving intensity

exhibited overall a slower decrease over the first two-weeks of treatment and craving was more variable from moment to moment in daily life. This may give a hint as to the mechanism by which craving responded less to treatment for the relapse group. The lower craving inertia (higher moment to moment craving variability) may translate the persistence of craving reactivity to cues and other everyday life triggers, which was not the case for the participants who will be in the remission group, and for which craving was more stable from moment to moment, possibly less influenced by cues and everyday life triggers, and consequently decreased more over the same 14-day period of treatment aiming at reducing craving and substance use. Until now, inertia measures were mainly used in studies on affect and mood (Houben, Van Den Noortgate et al. 2015, Buu, Cai et al. 2021, Morawetz, Berboth et al. 2022). More recently, some studies explored craving dynamics, and reported that greater craving instability was significantly linked to higher substance use in the same day (Chirokoff, Abdallah et al. 2022), and greater proportion of days of use during a 6-week study period (Ellis, Mun et al. 2022). However, these studies did not report significant associations between craving inertia and substance use. To our knowledge, this study is the first to explore the association of craving level dynamics with long-term outcomes. Our result suggests that craving dynamics, and particularly low craving inertia, could represent a prognostic indicator for reduced treatment response and further relapse. The slower decrease in craving as trajectory at the treatment initiation could express resistance to treatment that may have many mechanisms, among which a persistent reactivity to cues, and this increased vulnerability to cues could persist over time, and thus lead to more relapse in the long-term (Janes, Pizzagalli et al. 2010).

Interestingly, in this study, the strength of the craving-use association at treatment initiation was not found significantly different according to relapse status at 5+ years, suggesting that participants with a stronger craving-use link are not necessarily at greater risk of long-term relapse. In the same way, more intense craving at the beginning of treatment was not found associated with a greater risk of relapse at 5 years. This appears contradictory to a study that reported that patients with alcohol use disorder who relapsed after 12 months had significantly higher craving intensity at the end of a 3-month treatment episode (Bottlender and Soyka 2004). However, in this study, craving was assessed after a period of 3 months of treatment completion, and not at treatment intake. Two studies on tobacco also

showed that greater craving intensity at treatment intake was associated with less abstinence at one month (Cofta-Woerpel, McClure et al. 2011), and 6 months (Piper, Federmen et al. 2008). The difference with our results could be explained by the fact that firstly, these studies examined relapse status at short-term while our study explored at a much longer term; secondly, we looked at a post-quit period, i.e., at the beginning of treatment and during 2 weeks in daily-life by EMA. Some of these studies did not explore craving at the treatment initiation (Bottlender and Soyka 2004) or by EMA monitoring periods that may have been too short (seven-days post-quit) (Cofta-Woerpel, McClure et al. 2011).

Some limitations have to be acknowledged. The first limitation is related to how relapse was operationalized, based on primary substance use status at one time point, 5 years or more after treatment initiation. This particular state may not reflect the overall outcome over the 5-year period for all participants. Unfortunately, despite regular follow-ups, systematic information about eventual intermediate relapses was not available for all participants. We cannot exclude that different results could have been obtained by taking into account different time periods for relapse measures. However, it is clear that the relapse group is clinically significantly different from the remission group on addiction severity and substance use. Although both groups presented reduced addiction severity and substance use compared to baseline, the relapse group is using on average every other day (16.6 (12.5) days vs. 0) and addiction severity (ASI severity: 3.5 vs. 0.9) is that of a group still actively using and with important severity. Nonetheless, even if a majority of participants in the relapse group reported frequent use and higher addiction severity compared to the remission group, it is possible that some participants regained a moderate and possibly controlled use (Witkiewitz, Wilson et al. 2019).

Another potential limitation is the small sample size. However, this did not enable us to test the influence of potential confounding factors, including age, sex, medication and substance type. It is important to note that substance type was associated with a difference in craving intensity (less intense in the alcohol group) and primary substance use (less frequent in the opiates group; see Supplementary Table S3), but substance type was not associated with relapse, craving-use relationship, craving trajectory, nor craving dynamics parameters. This is consistent with literature suggesting that craving occupies a central place

in addiction (Kervran, Shmulewitz et al. 2020, Gauld, Baillet et al. 2023), across substances (Vafaie and Kober 2022), and influences use and relapse across addiction types (Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2015, Serre, Fatseas et al. 2018, Vafaie and Kober 2022). Furthermore, a recent fMRI study highlighting common neural substrates across different substances and palatable food (Vafaie and Kober 2022, Koban, Wager et al. 2023, Kronberg and Goldstein 2023) strongly suggesting craving may be a transdiagnostic indicator across addictions (Miele, Cabé et al. 2023).

Another limitation is that, in this study, only linear trends were tested in craving trajectory during the first 14-day of treatment. It would be interesting to explore other trajectories such as high- or low-craving groups or more complex patterns (Burgess-Hull, Panlilio et al. 2022), to explore whether some of them are more associated with long-term outcomes. Finally, our finding should be interpreted with caution due to the limited sample size, and the study findings need to be replicated in other settings.

Taken together, these results illustrate the utility of properly capturing craving dynamics and trajectory over time at treatment initiation, as they could provide valuable indicators of long-term outcome and relapse, and not just craving intensity. Indeed, if immediate craving intensity is logically associated with initiation of substance use in short intervals of time, on the contrary, over longer periods of time, it is rather the way in which craving is modulated by the environment, the treatment, or managed by the participant, which is a more stable characteristic, that is more likely to provide information on what an individual might experience in a more distant future. Such prognostic markers of long-term outcomes exist for other chronic conditions in medicine and psychiatry (McLellan, Lewis et al. 2000), but remain to be determined for addiction. Changes in craving at the start of treatment may be a greater reactivity to cues, making the individual more vulnerable to cues which could persist overtime and represent early indicators of SUD progression. Such indicators may help clinicians to anticipate and provide adjustment in treatment provided (frequency, duration) and resource allocation, in order to reduce the increased risk of poorer outcome. From a therapeutic point of view, mobile technologies, such as smartphone apps, could offer accessible, easy-to-use, and autonomous measures of symptoms dynamics in daily life (Dulin and Gonzalez 2017, Bahadoor, Alexandre et al. 2021, Serre, Moriceau et al. 2023), that could

also be used to detect the most appropriate moments to propose interventions (Nahum-Shani, Smith et al. 2018).

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Conflict of Interest

None to declare

AUTHORS CONTRIBUTIONS

Marc Auriacombe was the overall principal investigator and study supervisor, obtained funding and access to participants. Marc Auriacombe, Fuschia Serre, Melina Fatseas and Joel Swendsen developed the EMA study design and methods. Emmanuelle Baillet and Fuschia Serre conceptualized and conducted the analyses, interpreted the data, and wrote the manuscript. Cassandre Romao and Christophe Gauld helped in HLM analysis. Helene Garnier and Chloe Vacher helped for literature review and patient inclusion. All authors undertook the critical revision of the manuscript for important intellectual content and all authors significantly contributed to the manuscript and approved the final version.

ADDITIONAL INFORMATION

See SUPPLEMENTARY MATERIALS

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Table 1. Description of the sample

Sample characteristics	All participants (N=39)		Remission (N=19)		Relapse (N=20)		p value
	% (n)	Mean (SD)	% (n)	Mean (SD)	% (n)	Mean (SD)	
BASELINE							
Primary substance							
Alcohol	43.6 (17)		31.6 (6)		55.0 (11)		0.200
Tobacco	23.1 (9)		21.1(4)		25.0 (5)		1.0
Cannabis	25.6 (10)		31.6 (6)		20.0 (4)		0.480
Opiates	7.7 (3)		15.8 (3)		0		0.106
Sex (male)	69.2 (27)		68.4 (13)		70.0 (14)		1.0
Employed	61.5 (24)		63.2 (12)		60.0 (12)		1.0
Age		35.9 (11.3)		36.5 (12.2)		35.3 (10.5)	0.822
Education (years)		13.1 (3.3)		13.2 (4.1)		13.1 (2.5)	0.523
Days of primary substance use (past 30 days)		25.3 (8.3)		25.3 (7.5)		25.2 (9.2)	0.581
ASI addiction severity (0-9)		6.5 (0.7)		6.5 (0.7)		6.5 (0.6)	0.854
Medication	78.9 (30)		68.4 (13)		89.5 (17)		0.232
MINI addiction severity		6.1 (1.4)		6.0 (1.7)		6.1 (1.2)	0.885

Mood disorder	38.5 (15)		31.6 (6)		45.0 (9)		0.514
Anxiety disorder	38.5 (15)		31.6 (6)		45.0 (9)		0.514
FOLLOW-UP							
Average time between treatment initiation (EMA study) and follow-up (months)		77.7 (12.7)		78.0 (12.7)		77.5 (13.0)	0.767
Days of primary substance use (past 30 days)		8.5 (12.2)		0		16.6 (12.5)	<0.0001
ASI addiction severity (0-9)		2.3 (1.9)		0.9 (1.0)		3.5 (1.8)	<0.0001
Still receiving addiction treatment	51.3 (20)		52.6 (10)		50.0 (10)		1.0

Comparison between relapse vs. Remission status: Test Fisher for qualitative variables and Wilcoxon Test for quantitative variables.

Table 2. Description of daily life variables during EMA study

EMA variables	All participants (1497 observations)		Remission (705 observations)		Relapse (792 observations)		p-value
	% (n)	M (SD)	% (n)	M (SD)	% (n)	M (SD)	
Primary substance use	34.0 (509)		33.9 (239)		34.1 (270)		0.843
Other substances use	59.9 (897)		66.8 (470)		53.9 (427)		0.259
Craving episodes (intensity>0)	67.4 (1009)		76.9 (542)		58.9 (467)		0.082
Craving intensity (1-7)		3.4 (2.1)		3.7 (2.1)		3.1 (2.2)	0.775

Means-as-outcome models with relapse as predictor of EMA variables. All empty models were controlled on age, sex, medication and substance type. If model was significant, confounding factor was inserted in model.

Table 3. Cross-level interaction of relapse status at 5+ years follow-up on craving trajectory at the beginning of treatment (N = 39).

Predictor	Outcome	γ Coef	SE	df	T-ratio	p-value
Day in study	Craving	-0.05	0.02	38	-2.60	0.013
Interaction term: Relapse		0.08	0.04	37	2.10	0.043

Bold values indicate statistically significant P values. All models were controlled on age, sex, medication and substance typ

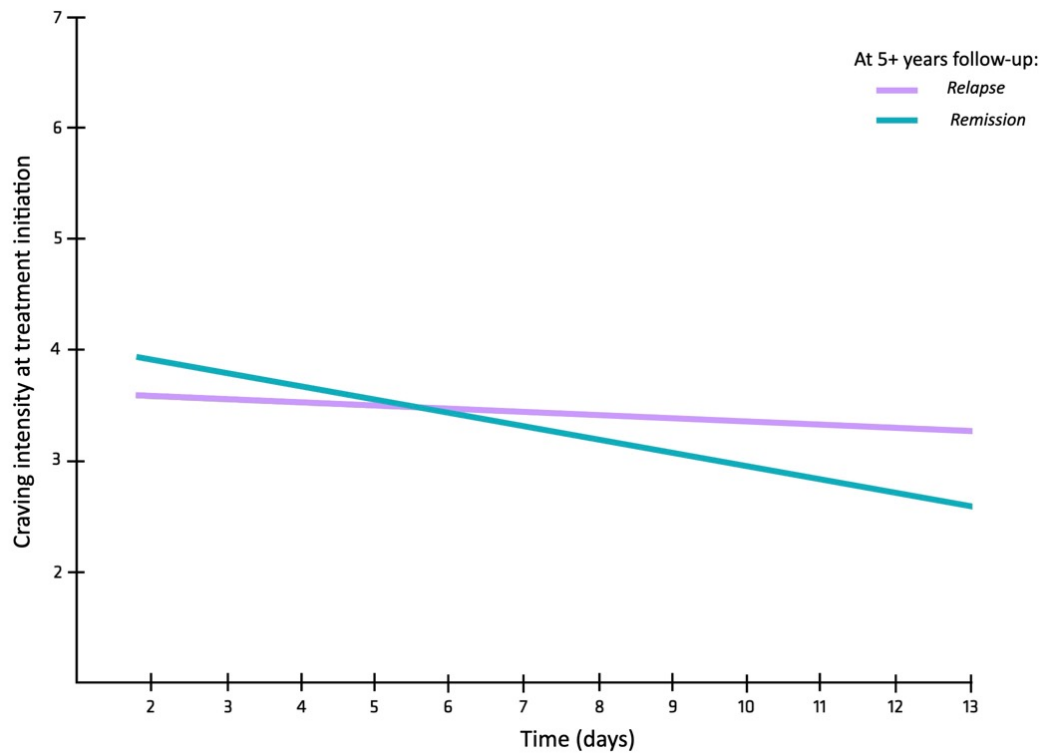


Figure 1. Craving trajectory over time in first days of treatment according to relapse status at 5+ years follow-up.

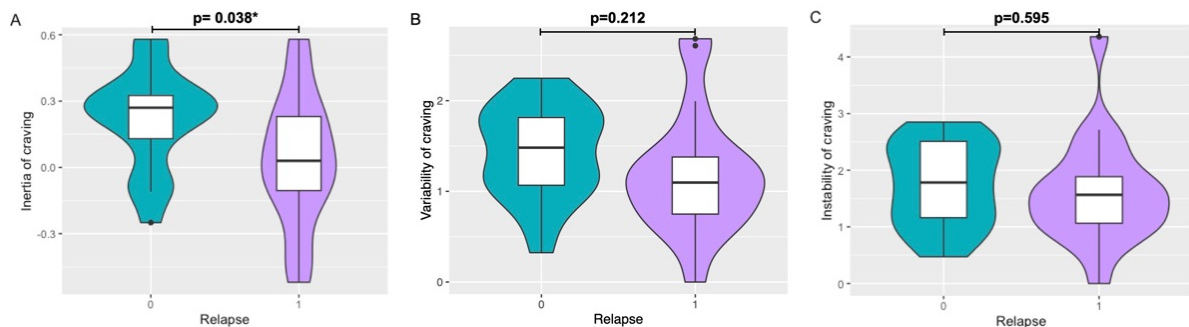


Figure 2. Metrics of craving dynamics during first days of treatment according to relapse status at 5+ years follow-up.

A) Craving inertia (AR1) for remission mean=.22 (SD=.22) vs relapse group mean=.03 (SD=.29); B) Craving variability (SD) for remission mean=1.43 (SD=.51) vs relapse group mean=1.19 (SD=.66); C) Craving instability (rMSSD) for remission mean=1.75 (SD=.73) vs relapse group mean=1.61 (SD=.92). All analysis has been performed with controlling on average intensity of craving.

MANUSCRIPT 4:

“The Autonomic Craving Signature: a pattern of physiological signals associated with craving in daily-life among tobacco, alcohol and cannabis users with SUD”

Submission in progress

The Autonomic Craving Signature: a pattern of physiological signals associated with craving in daily-life among tobacco, alcohol and cannabis users with SUD

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Conflict of interest

We report no conflicts of interest related to this work. The researchers confirm their independence from funders and sponsors.

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ABSTRACT

Context: Craving is a strong predictor of use and relapse across different substance use disorders (SUD). Identifying and reporting craving can be difficult for some patients highlighting the need for biomarkers, currently lacking. The aim of this study was to determine a robust methodology for the detection of craving based on physiological measurements captured in daily-life from the combination of ecological momentary assessment (EMA) and wearable sensors among participants with SUDs.

Participant and methods: Individuals with SUD were enrolled in a daily-life study in which craving reported at signal-contingent EMA and at event-contingent by initiation of users, as well as physiological signals [Electrodermal activity (EDA), accelerometer (ACC), skin temperature (TEMP), blood volume pulse (BVP)] were recorded continuously. After labeling “craving” and “no-craving” samples, features of each signal were extracted, normalized, standardized and filtered. Then, a principal component analysis (PCA) was applied. The linear combination of features [Principal Component (PC)] output was used to test several kinds of classifier algorithms.

Results: 43 participants (24 women, 19 men), with a mean age of 32.9 (SD=9.4) years were included for tobacco (n=20, 46.5% of the sample,), cannabis (n=14, 32.5%,) and alcohol (n=9, 20.9%,). EMA completion rate was 85.8% (n=2,017) and in total, 5,512 hours of physiologic data was captured over the course of 14 EMA-days. 384 samples of “craving” (n=192) and “no-craving” (n=192) were analyzed by PCA in which 31 principal components explained 98.8% of variance data. We tested 3 different classification algorithms with which we reached between 58.3% and 73.6% of accuracy.

Discussion and perspectives: Performance of our binary classification model was better than a random binary classifier (i.e.: AUC-ROC > 0.55) and this set of features forms a physiological pattern that can distinguish craving from no-craving states and that we labeled *the autonomous craving signature (ACS)*. This is an important breakthrough in the underlying neurobiological mechanisms of craving and paves the way for implications in clinical practice. For clinical practice, the passive detection of craving could be an important step in the development of biomarkers in SUDs.

INTRODUCTION

Substance use disorders (SUDs), the most prevalent and deadly forms of psychopathology (Steel, Marnane et al. 2014), may be defined by the loss or reduced control over use of rewarding substances and behaviors that translates into repeated and excessive use and relapses (American Psychiatric Association 2013, Hasin, O'Brien et al. 2013, Auriacombe, Serre et al. 2018b, Moe, Moltu et al. 2022). Craving defined as an unwanted persistent and intense desire to use could have a central role in SUD because it is a trigger of use and relapse across addictions (Serre, Fatseas et al. 2015, Auriacombe, Serre et al. 2018, Serre, Fatseas et al. 2018, Cavicchioli, Vassena et al. 2020, Vafaie and Kober 2022). Added as a SUD diagnostic criterion in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) (American Psychiatric Association 2013, Hasin, O'Brien et al. 2013, Auriacombe, Serre et al. 2018), it has been demonstrated to be central in network of DSM-5 SUD diagnostic criteria (Gauld, Baillet et al. 2023) and suggested to play a causative role in use and relapse (Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2015, Vafaie and Kober 2022), making it a potential etiologic marker of use in addiction. In addition to being a diagnostic criterion of addiction, craving is a fluctuating phenomenon (Sayette, Shiffman et al. 2000, Bujarski, Roche et al. 2015, Cleveland, Knapp et al. 2021) that can be captured by daily-life monitoring systems such as ecological momentary assessment (EMA) (Stone and Shiffman 1994). EMA, adapted and validated to study craving in SUDs (Serre, Fatseas et al. 2012), allows a real-time measurement of individual momentary states in the natural environment through repeated assessments overtime. Based on EMA research, a human model of addiction has been suggested across several substances and behaviors: the cues – craving – use model (Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2018, Auriacombe, Serre et al. 2018b). In this model, an increase in the number of cues in the environment is associated with an increase in the intensity of self-reported craving in the following EMA survey, itself associated with an increased likelihood of use in the following EMA survey, this craving - use link being unidirectional (Fatseas, Serre et al. 2015, Panlilio, Stull et al. 2019, Burgess-Hull, Panlilio et al. 2022, Ellis, Mun et al. 2022). At a neurobiological level, consistent with the cues – craving – use model, cue-reactivity paradigms lead to brain activity changes in some specific areas (e.g., amygdala, dorsal striatum, Ventral Striatum/NAc) (Volkow, Wang et al. 2006, Chase, Eickhoff et al. 2011, Kühn and Gallinat 2011). Cue-reactivity paradigms are protocols in which subjects are exposed in a human laboratory environment to substance-associated cues in one or more

sensory modalities that are used to induce craving while undergoing physiological monitoring or brain imaging (Ekhtiari, Zare-Bidoky et al. 2022). Recently, a study using fMRI reported a neurobiological craving signature (NCS), an fMRI neuromarker that predicted self-reported intensity of cue-induced craving (Koban, Wager et al. 2023). This fMRI neuromarker that included different brain areas (i.e., ventromedial prefrontal and cingulate cortices, ventral striatum, temporal/parietal association areas, mediodorsal thalamus and cerebellum) enabled discriminating substance users (with SUD and/or heavy users) from non-users based on NCS response to substance and food cues (Koban, Wager et al. 2023). This is a major step forward in the discovery of neuromarkers of craving and its neurobiological mechanisms. However, the fMRI protocol was built in order to study the effect of only one factor on another (e.g.: images of cues to induce craving), which makes the results difficult to transfer to real-life context, in which many factors (e.g.: social context or place) are likely to modify the phenomenon being assessed (Reichert, Gan et al. 2021). Moreover, fMRI is not accessible in daily-life for better understanding how laboratory observations generalize to everyday life and for translating NCS in clinical practice.

Psychophysiological measures, however, can be captured in daily-life to monitor changes in autonomic nervous system (ANS) regulation (Wang, Zhornitsky et al. 2019). The ANS regulates heart rate (HR), skin temperature (TEMP), breathing rates or electrodermal activity (EDA) which are commonly used as indicators of psychological arousal and can be captured by monitoring devices such as wearable sensors. Craving presents unique neurobiological changes which could express by increase in sympathetic nervous system (SNS) activity (Sinha, Fox et al. 2009). Several studies using the cue-reactivity paradigm have shown signs of physiological arousal such as a significant increase in HR, EDA, TEMP or accelerometer (ACC) and the appearance of craving at the same time (Childress, Ehrman et al. 1988, Carter, Lam et al. 2009, Sinha, Fox et al. 2009, Zhao, Fan et al. 2012, Trotzke, Starcke et al. 2014, Li, Wu et al. 2015, Buckner, Zvolensky et al. 2016). Interestingly, the magnitude of craving was correlated with these changes of activities suggesting that these physiological or brain activity changes could be the underlying biology of craving or its physiological expression (Volkow, Wang et al. 2006, Murphy, Lubman et al. 2018, Wang, Zhornitsky et al. 2019). Some studies have examined the physiological correlates of craving in human lab settings (Zhao, Fan et al. 2012, Gullapalli, Natarajan et al. 2019), others have described

ongoing protocols in daily-life (Boyer, Fletcher et al. 2012, Shi, Chen et al. 2015), but, to our knowledge, only 4 studies have published results from everyday life (Kennedy, Epstein et al. 2015, Chatterjee, Hovsepian et al. 2016, Carreiro, Chintha et al. 2020, van Lier, Noordzij et al. 2022).

In heroin and cocaine users, HR was significantly greater when participants reported craving than all other random periods measured by continuous monitoring (Kennedy, Epstein et al. 2015). An increase in HR recorded by wearable sensors was also found in patients with alcohol use disorders who reported craving in EMA (van Lier, Noordzij et al. 2022). Using wearable sensors during post-quit periods in smokers, a computational model to estimate craving (Chatterjee, Hovsepian et al. 2016) showed an accuracy of classifying craving self-reports of 73% using features from cardiovascular and respiratory parameters. In another study across several substances, craving was differentiated from no-craving episodes with accelerometry data by using machine learning algorithms with an accuracy of 76% (Carreiro, Chintha et al. 2020). This accuracy was increased to 82% when heart rate and EDA data were added in the algorithm. However, as mentioned by many authors of these studies, several limitations can impact the model development, accuracy, and reproducibility (Tackett, Brandes et al. 2019) and temper the impact of these results. First, craving cannot be identified with a single physiological parameter. At the current stage of knowledge, the use of one single physiological parameter (i.e., HR for (Kennedy, Epstein et al. 2015, van Lier, Noordzij et al. 2022)) may not be enough to identifying this complex phenomenon and a pattern of physiological measures (i.e., combination of HR, EDA and TEMP) maybe more appropriate. Indeed, the only neuromarker of craving identified to date consists of a pattern of several areas rather than a single structure (Koban, Wager et al. 2023) suggesting that the biology that underlies craving is too complex to be identified just with a single physiologic signal. Secondly, craving must be differentiated from confounding factors. Some variables that could influence the physiological measurements and produce potentially similar responses to craving could interfere with the measurements. Thus, some measures of craving may not be craving specific, but the association of different phenomena, such as stress co-occurring with craving (Kennedy, Epstein et al. 2015, van Lier, Noordzij et al. 2022) (Carreiro, Chintha et al. 2020)). Stress and craving have some physiological similarities (Sinha, Fox et al. 2009), and labeling a no-craving period from observation periods labeled as stress seems inappropriate

for differentiating craving from no-craving states. Third, to identify craving, the window time is very important. If it is too short, it might not be enough to identify craving, and would prevent the associated physiology from being captured in its entirety; if it is too long, it might take into account an event other than the craving episode, or the physiological changes might be masked because they would be diluted in too large an observation period. The length of the observation period, from 40 to 180 minutes in some studies, was chosen arbitrarily (Kennedy, Epstein et al. 2015, Carreiro, Chintla et al. 2020, van Lier, Noordzij et al. 2022), while some research suggest that craving episodes could be shorter, between 5 and 30 minutes (Heishman, Singleton et al. 2003, Shiffman, Shadel et al. 2003, Heishman, Saha et al. 2004, Niaura, Sayette et al. 2005, Heishman, Lee et al. 2010). Finally, craving needs to be explored with its fluctuations over time that will need experience-sampling methods (ESM) such as EMA with an adapted length of assessment (De Calheiros Velozo, Habets et al. 2022). The duration of the study must be long enough to capture enough events within individuals (Trull and Ebner-Priemer 2020) (e.g., 24 hours pre-quit and 72 hours post-quit (Chatterjee, Hovsepian et al. 2016) or 5 consecutive days only (Carreiro, Chintla et al. 2020) could be too short) and to collect sufficient data to be careful about missing data from non-compliance (Jones, Remmerswaal et al. 2019). To assess craving, the use of written-logs, where participants were instructed to report craving, stress or any physical activity in written at any time of the day, without specifying the immediacy of the annotation (Carreiro, Chintla et al. 2020), is at risk for more unreported episodes because data collection relies mostly on retrospective recall that may be prone to recall biases and errors.

To overcome these limitations, the aim of our study was to elaborate a robust methodology to determine the possibility of craving detection based on physiological signals (heart rate, electrodermal activity, skin temperature and accelerometry) captured in daily-life from the combination of EMA and wearable sensors among participants with SUDs. For this, we used a classification machine learning algorithm that is well-suited for predicting binary outcomes based on large feature sets, such as physiological data. We expected that the model would be able to classify craving vs. no-craving episodes, based on physiological and EMA data and that the model's performance would be significantly different from a random binary classifier (i.e.: $AUC-ROC > 0.55$ (Müller-Putz, Scherer et al. 2008, Nahm 2022)). This study will

be the first to study physiologic correlates of craving across substances in daily-life with the combination of EMA and wearable sensors, by using machine learning algorithm.

MATERIALS AND METHODS

Participants

To be eligible all participants had to be adults (>18 years), with at least one DSM-5 SUD (tobacco, alcohol or cannabis) and reported craving for that SUD in the past 30 days. Exclusion criteria were: pregnancy, cardiovascular disease, non-dominant upper extremity limitation (amputation or fracture), or psychiatric conditions incompatible with understanding protocol. The study was approved by French Regulation and ethical committee (CPP EST III, 2021-A01835-36) and all participants provided informed consent prior inclusion.

Experimental design

The study was a 14-day prospective observational study using daily-life methods: EMA and wearable sensors. During the enrollment visit, clinical assessment was provided with standardized tools such as the Addiction Severity Index (ASI) (Denis, Fatséas et al. 2016) and Mini International Neuropsychiatric Interview (MINI) (Sheehan, Lecrubier et al. 1998) to collect demographic and historical data about SUD and other psychiatric disorders. A brief training was performed with the sensor (wearing, using and charging) and EMA (using, understanding surveys). Participants were asked to wear the sensor on their non-dominant wrist all day for the duration of the study, and to remove it only to sleep. EMA surveys were adapted to the main addiction according to ASI and in case of poly-addiction, the choice was made with the participant. EMA measures used in the current investigation have been previously validated in samples with SUD (Serre, Fatséas et al. 2012). EMA surveys were presented 4 times/day in a random way, approximately every 3h30. At the end of test phase in daily-life, a debriefing was performed.

Ambulatory monitoring measures

Physiological parameters:

The E4® sensor (Empatica Inc., Cambridge MA, USA) is primarily a research device with good validity when compared to a reference device (Enewoldsen 2016, Schuurmans, de Looft et al. 2020, van Lier, Pieterse et al. 2020). This is a non-invasive wearable, in the form of a

wristband, which allows the continuous acquisition of physiological data in real time: blood volume pulse (BVP) (in beats/min (bpm) by photoplethysmography (Allen 2007)), electrodermal activity (EDA) (in microSiemens (μ S)), skin temperature (TEMP) (in Celsius degree ($^{\circ}$ C) by infrared thermophile) and 3-axis accelerometers (ACC) (in gravity (g)).

Craving measurements:

Craving was assessed both signal-contingent with EMA and event-contingent with wearable sensors. For the signal-contingent, craving was assessed on a 7-point numerical scale in EMA from “1” (not at all) to “7” (extreme craving) in response to the question "Since the last questionnaire, have you felt a desire to use [*main addiction*]?". For the event-contingent, participants were instructed to press the sensor button ('TAG') of sensor when they felt craving for their main addiction, regardless of intensity.

Analysis strategy

To meet our objective, a robust methodology was set up (Figure 1), each step of which is described below.

[FIGURE 1]

Sample labeling

To define classes of craving and no-craving, we used both craving reported in EMA and in sensor. “No-craving” class was defined when no craving was reported on the sensor (no-TAG) and no craving was reported on the corresponding EMA survey (intensity= 1); and “Craving” class was defined when craving was reported on the sensor (TAG) and craving was reported on the corresponding EMA (intensity>4 corresponding to the average intensity of the craving measurement scale). Periods when the participant mentioned stress (>1 on the EMA) were not taken into account in any of the classes (craving or no-craving). Other types of class existed, such as reporting craving on the sensor (TAG) but not on the corresponding EMA (intensity 1) or conversely. In the context of this study, these were not used. Then, we used epochs of 10 minutes to create our samples by class: epochs of 20 minutes randomly in the EMA periods corresponding to “no-craving” class and epochs of 20 minutes centered on a TAG (10 minutes before and after) in the EMA period corresponding to “craving” class. This

time window was based on the few studies that reported craving to last between 5 and 30 minutes by exploring its duration through acute administration of treatments/interventions in cue-response protocols (Shiffman, Shadel et al. 2003, Heishman, Saha et al. 2004, Niaura, Sayette et al. 2005, Zhong, Wu et al. 2006, Heishman, Lee et al. 2010) or through questionnaires (Heishman, Singleton et al. 2003).

Feature extraction

From each 20-minutes long epoch were extracted several features by domain types that characterize different aspects of the signal: time-, frequency- or non-linear-domains (Karthikeyan, Murugappan et al. 2012, Ralevski, Petrakis et al. 2019). This is an essential step that enables the reduction of the dimension of the signal and data compaction (Singh and Krishnan 2023). Based on the literature, we chose to be comprehensive to ensure a completeness of features (Boucsein, Fowles et al. 2012, Maxhuni, Muñoz-Meléndez et al. 2016, Nakajima, Lemieux et al. 2020, Habets, Herff et al. 2021, Lutin, Hashimoto et al. 2021, Shukla, Barreda-Ángeles et al. 2021, Tsai, Sue et al. 2021, Yang, Huang et al. 2021). All features are described with their definition and reference in the supplementary material (Table S1).

We standardized the features in order to place all features on the same scale and eliminate bias due to scale deviations during classification process. We proceeded to feature transformations by testing different possibilities using data from subjects with the largest total number of features (all classes combined) available. In our case, we used data from 5 subjects with 600 total samples. The different possibilities tested were: Distribution changes by transformation (6 possibilities: logarithm transformation, exponential transformation, square power transformation, cubic power transformation, root power transformation, quadratic power transformation) and robust standardization (2 possibilities). In all, 12 possibilities (6×2) were performed to improve and normalize features, i.e., for each feature, there was 12 transformed features. In order to obtain the most standardized features possible for further analysis, we calculated different metrics for each transformed feature: mean, standard deviation, quantile range (amplitude between percentiles 99% and 1%), kurtosis and skewness. For each feature, the transformed feature the closest to 1 of SD, closest to 0 of kurtosis and skewness and closest to 0 of mean was retained.

Feature filtering

To identify and eliminate features that may be less informative and do not contribute to performance, we rejected some features in case of the following criteria: (1) *low standard deviation (SD) (Min-max normalization)*: features with low SD $\leq 5\%$, i.e., those with little variation across dataset were filtered. To determine SD, each feature value was normalized based on the Min-Max Normalization (Salanke, Kumar et al. 2018) which allows value of features to be scaled within a specific range [0-1] or (2) *high correlation*: features highly correlated with threshold of ≥ 0.98 . The feature kept was the one with the best distribution and the closest scale to the other features.

Dimension reduction

The main aim was to simplify data representation while maintaining important features and eliminating noise or redundancy. This overcame the problems of the "curse of dimensionality", where a large number of features can lead to computational and modelling difficulties, as well as over-fitting problems (Poggio, Mhaskar et al. 2017). For this, we used the principal component analysis (PCA) (Abdi and Williams 2010) that works by identifying the principal directions or axes that capture the maximum variance in the data. These axes, called principal components (PCs), are ordered according to their ability to explain the total variance in the data (Migenda, Möller et al. 2021). Variance into data was examined regardless of class because PCA is a non-supervised algorithm, i.e., only variance into features data was analyzed, without Class labels. For a participant to be included in these between-individual analysis, the threshold was set at 20 samples/classes per participant. Then, the number of "craving" and "no-craving" samples had to be equal to maintain a balance. To achieve this, and to avoid the samples from the 2 classes differing in terms of time of day, the samples retained were selected as close as possible in time (for example, for a sample from the "Craving" class around midday, a sample from the "non-Craving" class was selected closest to midday). To decide how many PCs to retain in subsequent analysis, we chose to take a mixed method by using all criteria: scree Test, the Kaiser's rule and the proportion of variance explained to choose PC number that keep a maximum of variance data (Cattell 1966, Abdi and Williams 2010, Braeken and van Assen 2017). The number of PCs retained should contribute to the increase in the ratio of variance explained at the $\geq 0.001\%$ threshold. Then,

to describe features that contribute most to the first PCs, they were tested between the “craving” and “no-craving” classes with Student t test.

Model training and binary classification

To classify craving from no-craving samples, the performance of three classification models were tested at the between-individual level: Support vector machines (SVM), minimum distance to mean (MDM), linear discriminant analysis (LDA). SVM allows to find the best hyperplane to separate data points into different classes while maximizing the margin between them (Salcedo-Sanz, Rojo-Álvarez et al. 2014); MDM assigns a label to new data, placing it in the class whose average is closest in terms of distance (Vibhute, Dhumal et al. 2016); and LDA allows transforming features into a lower-dimensional space by minimizing the ratio of between-class variance to within-class variance, thereby ensuring maximum class separation (Graf, Zeldovich et al. 2022). The major aim was to project a space (N-dimensional data) onto a smaller subspace K ($K \leq n-1$). To prevent overfitting and having a great reliability of our classifier, a technique called k-fold cross-validation was applied (we choose $k=10$) (Wong and Yeh 2020). In our dataset, 80% were used for training and 20% as a test set. This process was repeated 10 times, each time using a different subset as the test set ensuring that the results were not influenced by a good/bad random subset. Then, the performance of model of test datasets were averaged and the results were obtained on a test set.

Evaluation of model performance

To evaluate our model performance, i.e., the ability of physiological data to distinguish classes: “craving” vs. “no-craving”, we considered the following standard metrics: specificity, recall, precision, accuracy and area under the curve (AUC) of the receiver operating characteristic (ROC) curve. To calculate these metrics, we used a confusion matrix, i.e., a table which describes the performance of classifiers by displaying the counts of true positive (TP), true negative (TN), false positive (FP) and false negative (FN) predictions (Baratloo, Hosseini et al. 2015). Then, we used the Area under the curve (AUC) of the receiver operating characteristic (ROC) curve. The ROC curve is a graphical representation of the relationship between sensitivity and specificity (Bradley 1997, Cross and Plunkett 2014). The AUC of the ROC curve ranges from 0 to 1: a model with an AUC of 1 indicates perfect performance, as it achieves a true positive rate of 1 (100%) and a false positive rate of 0 (0%). An AUC of 0.55

corresponds to a random guess, where the model's performance is no better than chance taking into account the number of trials and class applied here (Bradley 1997, Müller-Putz, Scherer et al. 2008, Cross and Plunkett 2014).

Permutation test

Permutation tests were employed to evaluate the statistical significance of classifier performance. These tests gauge the probability of achieving the observed classifier performance purely by random chance, stemming from patterns in the multi-dimensional data that coincidentally align with the membership labels due to the limitations of a small dataset size (Ganz and Konukoglu 2017). Consequently, permutation tests provide precise regulation of error rates. To estimate statistical significance of the cross-validation classifier accuracy for a α risk of 5%, we performed 100 randomized cross-validation iterations.

The proposed model was implemented using Python and R softwares and the following packages respectively: Librosa, Numpy, Pandas, Scipy, Neurokit2, Datetime, Colorama, Matplotlib, Seaborn, PyWavelets for Python and FactoMineR, MASS, for R. The codes used in this research are at: https://github.com/BioEMA_Project

RESULTS

Description of sample

From March 2022 to September 2023, 43 (95.6%) of 45 participants who signed the consent form provided sufficient data from wearing the sensor and answering the EMA, and were considered as the study sample for analysis. Participants of the study sample were aged 32.9 years (SD=9.4), and 55% (n=24) were woman. The main problem substance was tobacco (46.5% of the sample, n=20), followed by cannabis (32.5%, n=14) and alcohol (20.9%, n=9). On average they had 7.3 (SD=2.1) DSM-5 diagnostic criteria and a mean of 5.4 (SD=1.3) on the ASI severity score. Table 1 provides a description of the clinical characteristics of the sample and information concerning EMA.

[TABLE 1]

EMA completion rate was 85.8% (n=2,017) and the sensor was used on average 8.9 hours/day (SD=2.9). In total, 5,512 hours of physiologic data were captured over the course of EMA-days. The average craving intensity in signal-contingent EMA was 4.0/7 (SD=2.08) and among participants who initiated at least one craving-event on the sensor (TAG) (98%, n=42), the total number of craving-events was 1,654 TAGs with an average of 38.5 TAG (SD=33.4) per participant.

For labeling, 20-minutes of physiologic data were segmented from the original recordings: 1883 samples were labeled as “no-craving” and 1109 samples were labeled as “craving”. 4296 samples were not used in this study because they did not meet our labeling criteria (see Methods – sample labeling). From these selected samples, 190 features were extracted, normalized and standardized after which 98 were again rejected for missing values, high correlation or low standard deviation (Table S2 – Supplementary Materials). Consequently, each “craving” and “no-craving” samples was composed of a vector of 92 standardized and normalized features.

To maintain the balance between classes “craving” and “no-craving” and avoid overfitting, 384 samples of “craving” (n=192) and “no-craving” (n=192) from 5 participants who had at least 20 samples/classes were analyzed by PCA. As a result, 31 PCs, that explained 98.8% of variance data, were kept for the classification model (Figure S1 – Supplementary Materials). The first component (PC1) explained the majority of the total variance (73.8%) and the second component (PC2) explained 7.9% of the total variance. Five features of PC1 with greater weights (59.43% of PC1) (Figure S2 – Supplementary Materials) were significantly different between “craving” and “no-craving” classes: “EDA Tonic Min” (p<.0001), “EDA Tonic Mean” (p<.0001), “EDA Tonic Max” (p<.0001), “EDA Wavelet 0 RMS” (p<.0001), and “EDA Skew” (p=.020) (Table 2). In PC2, among five features with greater weights (42.27% of PC2) (Figure S3 – Supplementary Materials), “HRV SDNNI5” (p=.001), “HRV SDANN5” (p=.017), “HRV SDANN2” (p<.0001) and “HRV SDANN1” (p<.0001) were significantly different between “craving” and “no-craving”, but not “HRV DFA $\alpha 2$ ” (p=0.128) (Table 2).

[TABLE 2]

Then, the 31 PCs were used to perform SVM, MDM and LDA classifications and the results were obtained on a test set. Craving data set was designated as the positive class. For the MDM classifier, the sensitivity was 66.2% and the specificity was 51.0% (Fig. 2A). The AUC of the model's ROC was 0.58 (Fig. 2B) and the model's accuracy and precision were 58.3% and 55.5% respectively. For all measures, none of the permutation samples performed (accuracy score: 0.55) for as well as the observed results (all $p=0.02$) at the 95% confidence level (Fig. 5A). For the SVM classifier, the sensitivity was 74.5% and the specificity was 72.8% (Fig. 3A). The AUC of the model's ROC was 0.83 (Fig. 3B) and the model's accuracy and precision were 73.6% and 73.1% respectively. For all measures, none of the permutation samples performed (accuracy score: 0.56) as well as the observed results (all $p=0.01$) at the 95% confidence level (Fig. 5B). For the LDA classifier, the sensitivity was 76.8% and the specificity was 67.7% (Fig. 4A). The AUC of the model's ROC was 0.83 (Fig. 4B) and the model's accuracy and precision was 72.2% and 69.8% respectively. For all measures, none of the permutation samples performed (accuracy score: 0.55) as well as the observed results (all $p=0.01$) at the 95% confidence level (Fig. 5C).

[FIGURE 2]

[FIGURE 3]

[FIGURE 4]

[FIGURE 5]

DISCUSSION

Our aim was to develop a robust methodology for the detection of craving based on physiological signals captured in daily-life from the combination of EMA and wearable sensors among participants with SUDs. Using machine learning algorithms, our findings show that SVM and LDA classifiers were able to classify episodes of craving vs. no-craving with a cross-validation accuracy of 73.6% (sensitivity=74.5%, specificity=72.8%, AUC=0.83) and 72.2% (sensitivity=76.8%, specificity=67.7%, AUC=0.83) respectively. Thus, performance of SVM and

LDA models were better than a random binary classifier (i.e.: AUC-ROC > 0.55 (Müller-Putz, Scherer et al. 2008, Nahm 2022)).

This study is the first to develop a generalizable method to detect craving from physiologic signals across substances in daily-life. Extracting information from high dimensional physiologic data can be challenging and demands significant computational and space complexity. Due to a robust methodology and a rigorous approach, our study provides reliable results. The application of features selection and PCA provided significant advantages for pattern recognition tasks, such as craving (Prasad and Bruce 2008). PCA allowed to calculate principal component (PC), i.e., a linear combination of physiological features that was able to distinguish between craving and no-craving episodes. First PCs reflect a combination of features that explain the separation of “craving” from “no-craving” episodes and gives us a physiological pattern to identify craving. These features were mainly extracted from EDA and HR. Specifically, the PC1 explained the majority of the total variance (73.8%), i.e., the separation of craving and no-craving and was mainly composed by EDA features such as “EDA Tonic Min”, “EDA Tonic Mean”, “EDA Tonic Max”, “EDA Wavelet 0 RMS” and “EDA Skew”. The “EDA Wavelet 0 RMS” feature was extracted by Wavelet Transformation, and could be broken down into different frequency and time scales, for analysis of sudden, short-term signal changes (Cvetkovic, Übeyli et al. 2008). The fact that this feature was found in the pattern dissociating craving from no-craving, and that there was also a statistically significant difference, suggests that it is involved in the identification of the physiologic process related to craving. The “EDA Skew”, derived from the phasic component of EDA measured by the skin conductance level (SCL), corresponds to EDA distribution for the activity and more positive values indicate a peak of activity (Romine, Schroeder et al. 2022), which was found in craving episodes. This is potentially important, especially for the interaction with other features such as “EDA Tonic Min”, “EDA Tonic Mean” and “EDA Tonic Max” that were extracted from the tonic component. Tonic component reflects the overall arousal level of an individual in the absence of specific stimuli, while phasic component refers to faster changes caused by sudden emotional arousal or external stimuli (Benedek and Kaernbach 2010, Boucsein, Fowles et al. 2012). In line with our results craving might induce an activity peak reflected by the phasic component, but there seems to be an association with the tonic component which gives us both information on the general state of arousal and on a specific response to craving. Indeed,

the phasic component receives the most attention especially in cue-reactivity paradigms while it reflects a small part of the overall EDA complex and may not play an important role regarding the significance of specific features of EDA (Braithwaite, Watson et al. 2013, Shukla, Barreda-Ángeles et al. 2021). Although cue-reactivity craving-induced protocols are effective to develop our knowledge on craving and the neurobiology of addiction (Zilverstand, Huang et al. 2018) it does not take into account craving triggered by something other than cues, i.e., internal stimuli such as emotions or body sensation, or the unprovoked state of craving, i.e., “spontaneous” craving. Beyond the reactivity to cues in lab or natural settings, craving is a special state associated with addiction and could be reflected in basal levels of autonomic arousal. Our hypothesis based on these results would be that even in the absence of craving, individuals with addiction have a higher basic autonomic arousal (tonic component of EDA), that is increased in case of craving (phasic component of EDA). This phenomenon is particularly common in generalized anxiety disorder characterized by a high level of HR and EDA at rest (Pruneti, Saccò et al. 2016). Craving could be a sign of poor activation of the autonomic system at rest, i.e., a basal elevation of certain parameters such as HR and EDA and a high arousal at rest. This basal level, which is already high in individuals, increases during craving episode, making it possible to distinguish it from non-craving episodes.

This is an important breakthrough in the underlying neurobiological mechanisms of craving. This set of features forms a physiological pattern, which we label as *the autonomous craving signature (ACS)*, that distinguishes craving from no-craving states. ACS could present sufficient consistency and specificity of autonomic changes during craving episodes. The consistency is defined as a response that differs from a baseline condition (Quigley and Barrett 2014) and the specificity refers to the degree to which a particular emotion induces a unique and distinguishable physiological response (Quigley and Barrett 2014). To assess the consistency, we performed a statistical test between craving (test) and no-craving (control) with the two-conditions significantly different for each feature. As this was a study in daily-life, the individuals were not in the same places and did not encounter these 2 conditions at the same times (time within-day or between-days) which reinforces the consistency of ACS (Quigley and Barrett 2014), i.e., the physiological pattern that was able to distinguish craving from no-craving in daily-life, under any condition. Concerning the specificity, the way in which we performed a double-selection with the EMA signal contingent (retrospective measure) and

the participant-initiated event contingent (immediate measure) enabled us to guarantee that the craving episodes reported by the individual were really cravings, and to approach the validity of physiologic responses of these episodes in everyday life. Added to this, the elimination of samples associated with stress allows us to hypothesize good specificity. In addition to consistency and specificity, identifying a pattern rather than a single physiological parameter may be more suitable for identifying a phenomenon such as craving. Firstly, because natural physiology follows a rhythm that can cause a single parameter to vary, and that may not present good validity for what is being measured. For example, temperature can be affected by circadian rhythms, which are controlled by an internal biological clock interacting with the amount of wakefulness (Monk, Buysse et al. 1997). Thus, the use of a composition of several physiological parameters can reduce the impact of these internal variations. An important point is that we have detected a distinction between craving and no-craving with ACS, i.e., we take into account a control condition (no-craving) which has been double-checked just like the test condition (craving). Furthermore, as each individual is his own control, our model takes into account both intra- and inter-individual variability. Our findings indicate that features that composed the ACS had a significant difference between our 2 conditions (craving vs. no-craving). This model allows us to take into account the natural variation of autonomic system and excludes the hypothesis that the ACS could result from these variations. Moreover, although additional analyzes must be carried out, in particular on the fact that the ACS which distinguishes craving from no-craving is different from a pattern which distinguishes stress from a period of no-stress, the use of a pattern rather than only individual physiological parameters reinforces the specificity. In fact, the pattern makes it possible to overcome *Laws of Autonomic Constraint* which describes limitations of innervation of ANS and their reciprocal functioning (e.g., sympathetic activation is accompanied by parasympathetic withdrawal, or inversely) (Berntson, Cacioppo et al. 1991). Indeed, there are other modes of operation, which may occur frequently (Paton, Nalivaiko et al. 2006), and the isolated use of a single physiological parameter does not allow these changes in the 2 underlying autonomic inputs to be taken into account (Quigley and Barrett 2014). While we do not rule out the possibility that some of the features included in the ACS pattern are linked to other phenomena we cannot control, our hypothesis is that the combination of these markers makes the set specific and provides information on the physiological nature of craving. Taken together, these findings suggest the existence of a

specific common pattern between individuals, in daily-life, from activation of the autonomic system, mainly through cardiac and electrodermal activity, opening the way to better understanding the underlying mechanisms of craving, in particular the link with the ANS.

In addition to paving the way to a better understanding of the mechanisms of addiction and craving, this study has implications for clinical practice, diagnosis and treatment. The identification of craving regardless of the individual's awareness could be an important step in the development of prognosis biomarkers of use, in the same way that self-reported craving does. Overall, this study indicates that the use of our pattern, i.e., ACS, could detect craving in daily-life. This may be helpful to promote the long-term monitoring of craving without the need for the patient to engage in an effortful awareness that is likely to be difficult to sustain on the long run. The development of a passive detection of craving would be a significant advancement by reducing patient burden. Furthermore, the passive detection of craving would be useful for individuals with low insight of their substance-seeking behaviors or with difficulty in reporting craving (Goldstein, Craig et al. 2009, Lambert, Serre et al. 2021), which is associated to poor treatment outcome (Rinn, Desai et al. 2002, Cavicchioli, Vassena et al. 2020, Lambert, Serre et al. 2021). The ACS paves the way to the development of protocols of daily-life craving regulation that could constitute in the future a warning system that would be activated when this pattern is present both to warn the user and to promote a better insight and also to allow a relay towards care if needed or towards a just in time intervention (Serre, Moriceau et al. 2023). The regulation of craving is a key mechanism of successful treatment outcome across addictions (Kober and Mell 2015) and this system could allow a better prevention of relapse.

Important limitations have to be acknowledged. The main limitation is our choice of epoch length to create "craving" and "no-craving" samples that was of 20 minutes which was based on only few studies. In our study, this threshold of 20 minutes, centered on the participant self-initiated TAG, brought us closer to the phenomenon of craving to avoid its consequences. Indeed, it could be important to consider craving both as a clinical symptom and a brain function and thus, to distinguish its appearance, the phenomenon of craving itself and its consequences. Thus, the longer the time, the more the expression of the consequences of craving may take the lead on physiological expression. Despite our

significant results on physiologic manifestation of ANS, the temporality of craving and its duration remains to be explored further and could be tested in future investigations. This study was a first step in determining whether the identification of craving by wearable physiological generated data was feasible in real-life conditions. The main difficulty lay in balancing craving and no-craving data. The majority of participants had either not enough episodes of no-craving, or not enough episodes of craving. To overcome these difficulties, the number of signal-contingent EMAs (4 in the current protocol) could be increased. Furthermore, our study was based on only 2 of the most restrictive types of craving classes (consistent classes), whereas inconsistent classes do exist. It might be interesting to explore, in future analyses, how our ACS model classifies these inconsistent craving classes. We wanted to use the best current techniques while being as comprehensive as possible. Our model allows both intra- and inter-individual variability to be taken into account, suggesting the reproducibility of the model (Tackett, Brandes et al. 2019) and its results. Moreover, we choose low thresholds for correlation (≥ 0.98) or standard deviation ($\leq 5\%$). Thus, even if we are not too strict, our results indicate a classification of around 75%, suggesting that the detection of craving is both possible as shown by our findings and could be improved by setting more restrictive thresholds. Further analysis could explore, as suggested by authors of previous research (Koban, Wager et al. 2023), how the ACS – physiological pattern of craving – may be associate with the NCS (Koban, Wager et al. 2023).

Conflict of Interest

None to declare

AUTHORS CONTRIBUTIONS

Marc Auriacombe was the overall principal investigator and study supervisor, obtained funding and access to participants. Marc Auriacombe, Emmanuelle Baillet, Fuschia Serre developed the study design and methods. Emmanuelle Baillet set up the study, included the participants, conducted the analyses, interpreted the data, and wrote the manuscript. Thibaut Monseigne helped in analysis and data management. Hakim Si-Mohammed and Camille Jeunet helped in the conceptualization of analysis, in architecture of classification model and in the interpretation of data. All authors undertook the critical revision of the

manuscript for important intellectual content and all authors significantly contributed to the manuscript and approved the final version.

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TABLE AND FIGURES

Table 1. Characteristics of the sample and description of daily-life variables.

	% (N)	M (SD)	Min	Max
<i>Samples characteristics (N=43)</i>				
Gender (woman)	55 (24)			
Employed	76.2 (32)			
Age		32.9 (9.4)		
Education (years)		14.5 (1.9)		
<i>Main problematic substance use</i>				
Tobacco	46.5 (20)			
Cannabis	32.5 (14)			
Alcohol	20.9 (9)			
ASI severity		5.4 (1.3)	0	7
MINI SUD severity		7.3 (2.1)	0	11
<i>MINI current diagnosis</i>				
Mood disorder*	20.9 (9)			
Anxiety disorder*	20.9 (9)			
<i>Signal-contingent EMA (observations = 2,017)**</i>				
Main problematic substance use	51.4 (1037)			
Craving intensity (1-7)		4.0 (2.1)	0	7
Craving episodes (intensity>1)	77.2 (1556)			
Event-contingent sensor (>0)	1 654	38.5 (33.4)		

*Mood disorders includes major depressive episode, dysthymia and hypomania; Anxiety disorders includes social phobia, generalized anxiety disorder and panic disorder.

**Frequencies, percentages and means are based on the total number of valid electronic surveys during the assessment period. ASI = Addiction Severity Index; MINI = Mini International Neuropsychiatric Disorder; EMA = Ecological Momentary Assessment

Table 2. Description of the main features of the first PCs applied to craving/no-craving samples.

PC	Features	M (SD)[Craving]	M (SD)[No-craving]	t-ratio	dof	Prob.> t
PC1	EDA Tonic Min	2.59 (9.52)	11.65 (21.75)	-5.28	261.67	<.0001
PC1	EDA Tonic Mean	0.51 (0.89)	1.20 (1.36)	-5.86	329.5	<.0001
PC1	EDA Tonic Max	0.74 (1.01)	1.46 (1.38)	-5.82	349.8	<.0001
PC1	EDA Wavelet 0 RMS	0.20 (0.70)	0.82 (1.16)	-6.27	314.6	<.0001
PC1	EDA Skew	1.28 (3.05)	0.59 (2.78)	2.33	378.9	0.020
PC2	HRV SDNNI5	1.82 (4.89)	0.64 (1.38)	3.22	221.3	0.001
PC2	HRV SDNN5	0.98 (4.64)	0.16 (0.85)	2.41	203.8	0.017
PC2	HRV SDANN2	1.22 (2.62)	0.29 (1.65)	4.16	322.6	<.0001
PC2	HRV SDANN1	1.08 (1.92)	0.22 (1.24)	5.22	327.6	<.0001
PC2	HRV DFA $\alpha 2$	-0.20 (2.01)	0.04 (0.83)	-1.53	254.5	0.128

Unit of all EDA features was microSiemens (μS); second (s) for HRV SDANNI5, HRV SDANN5, HRV SDANN2 and HRV SDANN1 features; HRV DFA $\alpha 2$ had no unit.

Figure 1: Pipeline of methodology

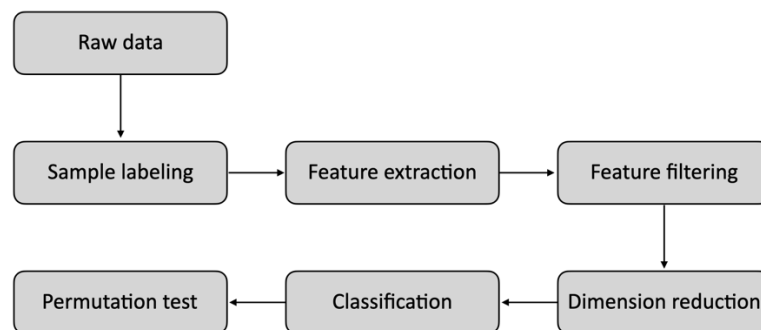


Figure 2: MDM Classifier performance. (A) Confusion Matrix; (B) ROC curve.

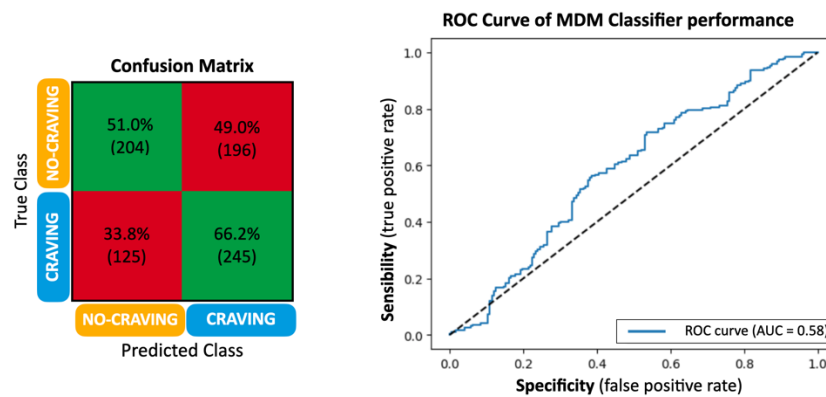


Figure 3: SVM Classifier performance. (A) Confusion Matrix; (B) ROC curve.

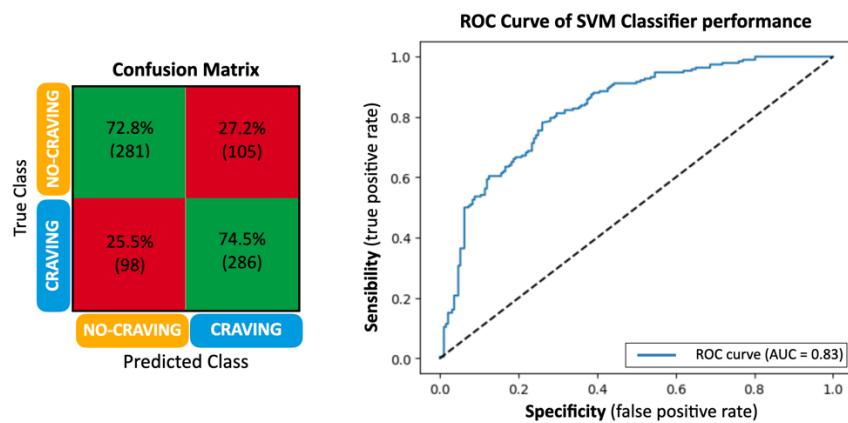


Figure 4: LDA Classifier performance. (A) Confusion Matrix; (B) ROC curve.

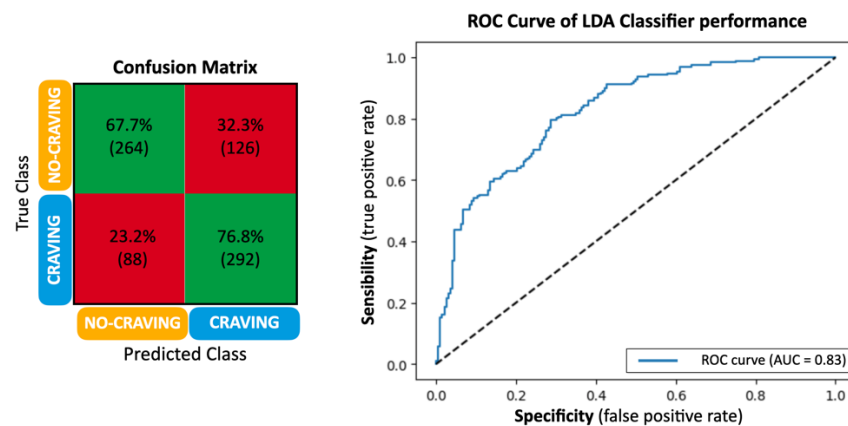
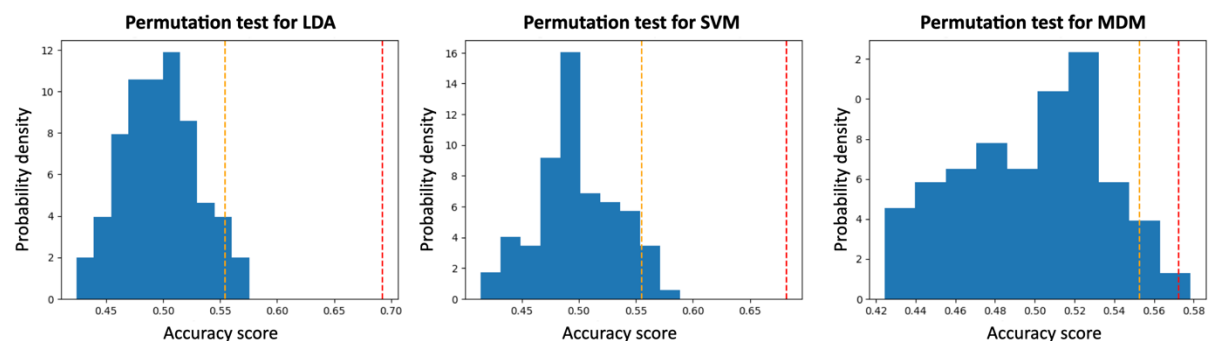


Figure 5: Permutation test results for LDA, SVM and MDM classifiers.



Permutation tests based on 100 iterations. Null distributions are plotted in blue bars, the 95th percentile of permutations accuracy as orange lines, observed accuracy measures as red lines.

Supplementary Material

The Autonomic Craving Signature: a pattern of physiological signals associated with craving in daily-life among tobacco, alcohol and cannabis users with SUD

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METHODS.

Table S1. Features extracted from all physiologic signals.

A total of 190 features from all the different signals were extracted: 109 features extracted from EDA raw data, 65 features from BVP raw data, 2 features from TEMP raw data, 12 features from ACC raw data and 2 from daily-life signal.

Feature name	Definition and formula if applicable	Unit	References
EDA signal			
<i>Time-domain features</i>			
Mean	Mean of signal: $\mu = \frac{1}{N} \times \sum_{i=1}^N EDA_i$	MicroSiemens (μS)	(Boucsein, Fowles et al. 2012, Simons, Doyle et al. 2020, Lutin, Hashimoto et al. 2021)
Std	Standard deviation of signal: $\sigma = \sqrt{\frac{1}{N} \times \sum_{i=1}^N (EDA_i - \mu)^2}$	μS	
Kurtosis	Shape of the curve relative to a normal distribution. A positive kurtosis indicates a sharper distribution (more concentrated around the mean) than a normal distribution, while a negative kurtosis indicates a flatter distribution (more spread out) than a normal distribution.	μS	
Skewness	Measure of the asymmetry of the distribution. Positive skewness indicates rightward asymmetry, which is indicative of peak activity.	μS	
Power	Power of signal. Mean of square values: $\omega = \frac{1}{N} \times \sum_{i=1}^N EDA_i^2$	MicroSiemens square (μS^2)	
SCR peak count	SCR peak counts	No unit	(Benedek and Kaernbach 2010, Simons, Doyle et al. 2020, Lutin, Hashimoto et al. 2021)
SCR Mean amplitude	Summed magnitude of the SCRs	μS	
SCR rise time	Summed of rise time SCR divided by peak counts	s	
SRC AUC	Summed area under the SCRs	MicroSiemens-seconds ($\mu S.s$)	
Tonic min	Minimum of tonic component	μS	
Tonic Max	Maximum of tonic component	μS	
Tonic Mean	Mean of tonic component	μS	
Tonic Std	Standard deviation of tonic component	μS	
Phasic Min	Minimum of phasic component	μS	

Phasic Max	Maximum of phasic component	μS	
Phasic Mean	Mean of phasic component	μS	
Phasic Std	Standard deviation of phasic component	μS	
Hjorth Activity	measures the overall level of signal activity. It is calculated by evaluating the average signal energy.	No unit	
Hjorth Mobility	measure of the signal’s average frequency, indicating the amount of rapid variation. It is calculated by evaluating the variation in the signal’s rate of change.	No unit	
Hjorth Complexity	measures the signal’s level of complexity or diversity. It is calculated by evaluating the variation in the signal’s rate of change.	No unit	
Frequency-domain features			
PSD Min	Minimum of spectral band powers in the [0.05-0.5] Hz bands	μS	(Pope, Mishra et al. 2018, Lutin, Hashimoto et al. 2021, Shukla, Barreda-Ángeles et al. 2021)
PSD Max	Maximum of spectral band powers in the [0.05-0.5] Hz bands	μS	
PSD Std	Std of spectral band powers in the [0.05-0.5] Hz bands	μS	
PSD Mean	Sum of PSD in the [0.05-0.5] Hz bands		
Energy Wavelet	Energy for wavelet levels [Absolute] [1-4]	μS	
Energy distribution	Energy percentage for wavelet levels [1-4]	μS	
Entropy Wavelet	Entropy for wavelet levels [1-4]	μS	
RMS Wavelet	Root mean square for wavelet coefficients [1-4]	μS	
Mean MFCC	Mean of MFCC coefficients [0-12]	μS	
Std MFCC	Standard deviation of MFCC coefficients [0-12]	μS	
Median MFCC	MFCC coefficients for all frames [0-12]	μS	
Kurt MFCC	Kurtosis of MFCC coefficients [0-12]	μS	
Skew MFCC	Skewness of MFCC coefficients [0-12]	μS	
HR signal			
Time-domain features			
Mean HR	Mean of heart rate μ_{HR}	Beats/min (bpm)	
Std HR	Standard deviation of HR σ_{HR}	bpm	

NN (not feature)	time interval between two consecutive R peaks with additional filter	Seconds (s)	(Nakajima, Lemieux et al. 2020, Maqsood, Xu et al. 2021, Park, Seok et al. 2021)
MeanNN	Mean of NN interval: μ_{NN}	s	
SDNN	Standard deviation of NNi: σ_{NN}	s	
MedianNN	Median of NN intervals: Me_{NN}	s	
MadNN	Standard deviation from median: σ_{Me}	s	
MCVNN	Median absolute deviation of NN intervals divided by median of NN intervals: $\frac{Mad_{NN}}{Median_{NN}}$	No unit	
MinNN	Minimal of NN intervals: $\min(NN)$	s	
MaxNN	Maximal of NN Intervals: $\max(NN)$	s	
rMSSD	root mean square of successive RR intervals differences: $\sqrt{\mu_{dif_{NN}}^2}$	s	
SDSD	the standard deviation of successive differences between NN intervals: $\sigma_{dif_{NN}}$	s	
CVNN	Standard deviation of NN intervals divided by mean of NN intervals: $\frac{\sigma_{NN}}{\mu_{NN}}$	No unit	
CVSD	Mean square root of successive differences divided by the mean of the NN intervals: $\frac{\sqrt{\mu_{dif_{NN}}}}{\mu_{NN}}$	No unit	
IQRNN	Interquartile range of RR intervals	s	
Prc20NN	The 20th percentile of RR intervals	s	
Prc80NN	The 80th percentile of RR intervals	s	
pNN50	Percentage of successive RR intervals that differ by more than 50ms	No unit	
pNN20	Percentage of successive RR intervals that differ by more than 20ms	No unit	
HTI	HRV triangular index, measuring the total number of RR intervals divided by the maximum height of the RR interval histogram	No unit	
TINN	Geometric HRV parameter, or more precisely, the base width of the RR interval distribution obtained by triangular interpolation, where the least-squares error determines the triangle. It is an approximation of the RR interval distribution	s	
SDANN1	Standard deviation of the mean RR Intervals over the period divided into 1-minute segments	s	
SDNNI1	Mean Standard Deviation of RR Intervals over the period, divided into 1-minute segments	s	

SDANN2	Standard deviation of the mean RR Intervals over the period divided into 2-minute segments	s	
SDNNI2	Mean standard deviation of RR intervals over the period, divided into 2-minute segments	s	
SDANN5	Standard deviation of the mean RR Intervals over the period divided into 5-minute segments	s	
SDNNI5	Mean Standard Deviation of RR Intervals over the period, divided into 5-minute segments	s	
Frequency-domain features			
HRV power ULF	Absolute Spectral Power of Ultra Low Frequencies ([0, 0.0033]): $PSD_{[0,0.0033]}$	s^2	(Nakajima, Lemieux et al. 2020, Maqsood, Xu et al. 2021, Park, Seok et al. 2021)
HRV power VLF	Absolute Spectral Power of Very Low Frequencies ([0.0033, 0.04]): $PSD_{[0.0033,0.04]}$	s^2	
HRV power LF	Absolute Spectral Power of Low Frequencies ([0.04, 0.15]): $PSD_{[0.04,0.15]}$	s^2	
HRV power HF	Absolute Spectral Power of High Frequencies ([0.15, 0.4]): $PSD_{[0.15,0.4]}$	s^2	
HRV power VHF	Absolute Spectral Power of Very High Frequencies ([0.4, 0.5]): $PSD_{[0.4,0.5]}$	s^2	
HRV LF/HF	Low / High frequency ratio: $\frac{PSD_{LF}}{PSD_{HF}}$	No unit	
HRV Power LFn	Normalized Absolute Spectral Power of Low Frequencies ([0.04, 0.15]): $\frac{PSD_{LF}}{PSD_{Total}}$	s^2	
HRV Power HFn	Normalized Absolute Spectral Power of High Frequencies ([0.15, 0.4]): $\frac{PSD_{HF}}{PSD_{Total}}$	s^2	
HRV Power log LF	Logarithmic Absolute Spectral Power of Normalized High Frequencies: $\log(Power_{LF})$	s^2	
Non-linear-domain features			
SD1	Standard deviation perpendicular to the identity line.	s	(Park, Seok et al. 2021)
SD2	Standard deviation along the identity line.	s	
SD1/SD2	Ratio SD1/SD2: $\frac{SD1}{SD2}$	No unit	
S	Ellipse zone described by SD1/SD2: $\pi \times SD1 \times SD2$	Second square (s^2)	
CSI	Cardiac Sympathetic Index is a measure of cardiac sympathetic function independent of vagal activity, calculated by dividing the	Not unit	

	longitudinal variability of the Poincaré diagram by its transverse variability: $\frac{4 \times SD2}{4 \times SD1}$		
CVI	Cardiac Vagal Index is equal to the logarithm of the product of longitudinal and transverse variability: $\log_{10}(4 \times SD1 \times 4 \times SD2)$	Not unit	
CSI modified	division of the square of the longitudinal variability by its transverse variability: $\frac{(4 \times SD2)^2}{4 \times SD1}$	Not unit	
PIP	Percentage of inflection points in the RR interval series	Not unit	
IALS	Inverse of the average length of acceleration/deceleration segments	Not unit	
PSS	Percentage of short segments	Not unit	
PAS	Percentage of NN intervals in alternating segments	Not unit	
ApEn	Approximate entropy	Not unit	
SampEn	Sampling entropy	Not unit	
ShanEn	Shannon Entropy	Not unit	
FuzzyEn	Fuzzy entropy	Not unit	
MSEn	MSE entropy	Not unit	
CMSEn	CMS Entropy	Not unit	
RCMSEn	RCMSE Entropy	Not unit	
CD	Fractal correlation	Not unit	
HFD	Fractal Higuchi	Not unit	
KFD	Fractal Katz	Not unit	
LZC	Lempelziv Complexity	Not unit	
GI	Guzik index, defined as the distance from points above the line of identity (LI) to LI divided by the distance from all points on the Poincaré line to LI, except those on LI	Not unit	
SI	Slope index, defined as the phase angle of points above LI divided by the phase angle of all points on the Poincaré plot, except those on LI	Not unit	
AI	Area index, defined as the cumulative area of sectors corresponding to points above LI divided by the cumulative area of sectors corresponding to all points on the Poincaré plot except those on LI	Not unit	
PI	Porta index, defined as the number of points below LI divided by the total number of points in the Poincaré diagram, excluding those on LI	Not unit	

C1d	Contribution of heart rate decelerations to short-term HRV.	Not unit	
C1a	Contribution of heart rate accelerations to short-term HRV.	Not unit	
DFA alpha1	Monofractal fluctuation analysis with no HR signal trend, corresponding to short-term correlations.	Not unit	
DFA alpha2	Monofractal fluctuation analysis with no HR signal trend, corresponding to long-term correlations.	Not unit	
TEMP signal			
<i>Time-domain features</i>			
Mean TEMP	Average temperature	Celsius (°C)	(Gielen and Aerts 2019, Simons, Doyle et al. 2020)
Std TEMP	Standard deviation of temperature	°C	
ACC signal			
<i>Time-domain features</i>			
Magnitude (not feature)	$Mag = \sqrt{x^2 + y^2 + z^2}$	Gravity (g)	(Maxhuni, Muñoz-Meléndez et al. 2016, Nakajima, Lemieux et al. 2020)
RMS	root mean square of the average of the acceleration data on the three axes (X, Y, Z). This is a measure of the overall amplitude of the acceleration signal: $RMS = \sqrt{\frac{1}{N} \times \sum_{i=1}^N x_i^2 + y_i^2 + z_i^2}$	g	
Mean of Magnitude	Euclidean norm of the acceleration vector, calculated as the square root of the sum of the squares of the acceleration data on the three axes (X, Y, Z). It's a measure of motion intensity, without taking direction into account: $\mu = \frac{1}{N} \times \sum_{i=1}^N Mag_i$	g	
Std	Standard deviation of magnitude: $\sigma = \sqrt{\frac{1}{N} \times \sum_{i=1}^N (Mag_i - \mu)^2}$		
Amplitude range	Difference between min-max of magnitude: $Range = Mag_{max} - Mag_{min}$	g	
Signal Magnitude Area	Sum of absolute values for each axis: $SMA = \sum_{i=1}^n x_i + y_i + z_i $	g	

Curve Length	Sum of the absolute differences between adjacent values in the magnitude: $CL = \sum_{i=2}^n Mag_i - Mag_{i-1} $	g	(Maxhuni, Muñoz-Meléndez et al. 2016, Nakajima, Lemieux et al. 2020)	
Non-linear energy	Mean of the differences between the square of the values and the product of the two adjacent values in the magnitude: $NLE = \frac{1}{N-2} \times \sum_{i=2}^{N-1} Mag_i^2 - Mag_{i-1} \times Mag_{i+1}$	g		
Frequency-domain features				
PSD (Not feature)	$PSD = \hat{S}_{Welch}(signal)$	g		
Tremors	Amount of vibration due to tremors ([3.5 - 7.5]): $Tremors = \sum PSD_{3.5-7.5}$	g		
FFT magnitude Normalized (not feature)	$FFT_{x_{mag}} = \frac{2}{windowsLength} \times \sqrt{FFT_{x_{real}}^2 + FFT_{x_{imag}}^2}$	g		
FFT Magnitude combined 3 axes (not feature)	$FFT_{mag} = \sqrt{FFT_{x_{mag}}^2 + FFT_{y_{mag}}^2 + FFT_{z_{mag}}^2}$	g		
FFT Energy (not feature)	squared sum of its spectral coefficients (sum of the squared discrete FFT component magnitudes of the signal) normalized by the length of the window: $FFT_{Energy} = \sum FFT_{mag}$	g ² /Hz		
FFT mean energy	Mean of FFT energy: $FFT_{\mu Energy} = \frac{1}{N} \times \sum_{i=1}^N FFT_{mag_i}$	g		
FFT Std energy	Standard deviation of FFT energy: $FFT_{\sigma Energy} = \sqrt{\frac{1}{N} \times \sum_{i=1}^N (FFT_{mag_i} - FFT_{\mu Energy})^2}$	g		
Peak power	maximum power observed in the FFT spectrum of the acceleration signal: $FFT_{PeakPower} = \max(FFT_{mag})$	g		

Peak frequency	Frequency with the maximum magnitude in the FFT spectrum: $FFT_{PeakPower} = \text{argmax}(FFT_{mag})$	g	
Daily-life signal			
<i>Time-domain features</i>			
Day	Separation of weekdays and weekends	No unit	(Cleveland, Knapp et al. 2021)
Time	Separation of daytime (8am to 4pm) and evening/night-time schedules	No unit	

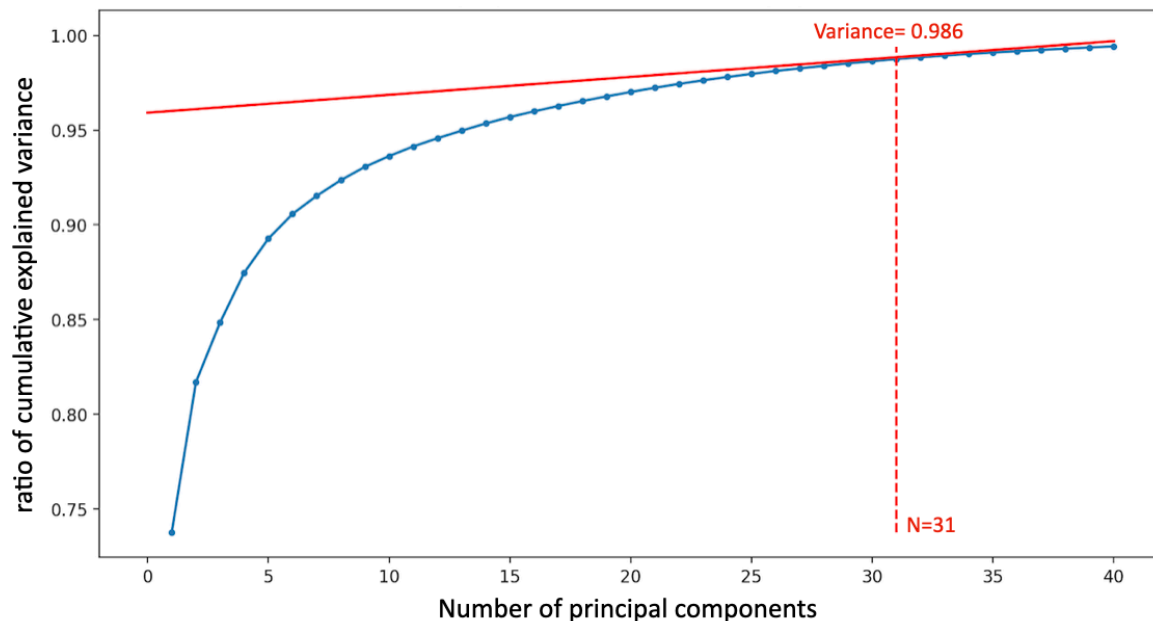
RESULTS.

Table S2. Results of features filtering

Cases of rejection	Number of features	Name of features
Low standard deviation ($\leq 5\%$)	22	"Accelerometer Peak Frequency", "EDA Kurtosis", "EDA MFCC 0 Std", "EDA MFCC 1 Std", "EDA MFCC 10 Std", "EDA MFCC 11 Std", "EDA MFCC 12 Std", "EDA MFCC 2 Std", "EDA MFCC 3 Std", "EDA MFCC 4 Std", "EDA MFCC 5 Std", "EDA MFCC 6 Std", "EDA MFCC 7 Std", "EDA MFCC 8 Std", "EDA MFCC 9 Std", "EDA Phasic Mean", "HRV AI", "HRV C1a", "HRV C1d", "HRV GI", "HRV SDANN1", "HRV SI"
High Pearson correlation (≥ 0.98)	24	["HRV C1a", "HRV C1d"]; ["EDA MFCC 11 Mean", "EDA MFCC 11 Median"]; ["EDA MFCC 4 Mean", "EDA MFCC 4 Median"]; ["EDA MFCC 7 Mean", "EDA MFCC 7 Median"]; ["EDA MFCC 8 Mean", "EDA MFCC 8 Median"]; ["EDA MFCC 9 Mean", "EDA MFCC 9 Median"]; ["EDA MFCC 10 Mean", "EDA MFCC 10 Median"]; ["EDA MFCC 5 Mean", "EDA MFCC 5 Median"]; ["EDA MFCC 12 Mean", "EDA MFCC 12 Median"]; ["EDA MFCC 2 Mean", "EDA MFCC 2 Median"]; ["EDA MFCC 3 Mean", "EDA MFCC 3 Median"]; ["EDA MFCC 6 Mean", "EDA MFCC 6 Median"]; ["EDA MFCC 1 Mean", "EDA MFCC 1 Median"]; ["EDA MFCC 0 Mean", "EDA MFCC 0 Median"]; ["EDA Mean", "EDA Power", "EDA Tonic Mean"]; ["HRV CVNN", "HRV CVSD", "HRV RMSSD", "HRV S", "HRV SD1", "HRV SD2", "HRV SDNN", "HRV SDNNI1", "HRV SDNNI2", "HRV SDSD"]; ["EDA PSD Max", "EDA PSD Mean", "EDA PSD Std"]; ["EDA Std", "EDA Tonic Std"]; ["HRV CVNN", "HRV CVSD"]; ["HRV SDNNI1", "HRV SDNNI2"]; ["Accelerometer FFT Std Energy", "Accelerometer Peak Power"]; ["Accelerometer Non-linear energy", "Accelerometer Tremors"]; ["EDA Phasic Max", "EDA Phasic Std"]; ["EDA Wavelet 1 Energy", "EDA Wavelet 1 RMS"]
High Spearman correlation (≥ 0.98)	34	["EDA MFCC 3 Mean", "EDA MFCC 3 Median"]; ["EDA MFCC 5 Mean", "EDA MFCC 5 Median"]; ["HRV CSI", "HRV SD1SD2"]; ["EDA MFCC 2 Mean", "EDA MFCC 2 Median"]; ["HRV Power HF", "HRV Power log HF"]; ["HRV CSI Modified", "HRV CVI", "HRV CVNN", "HRV CVSD", "HRV RMSSD", "HRV S", "HRV SD1", "HRV SD2", "HRV SDNN", "HRV SDNNI1", "HRV SDNNI2", "HRV SDSD"]; ["HRV CVI", "HRV S", "HRV SD2", "HRV SDNN", "HRV SDNNI2"]; ["EDA Power", "EDA Wavelet 0 Energy", "EDA Wavelet 0 RMS"]; ["EDA Wavelet 1 Energy", "EDA Wavelet 1 RMS"]; ["EDA Wavelet 2 Energy", "EDA Wavelet 2 RMS"]; ["EDA Wavelet 3 Energy", "EDA Wavelet 3 RMS"]; ["EDA Wavelet 4 Energy", "EDA Wavelet 4 RMS"]; ["HRV C1a", "HRV C1d"]; ["EDA MFCC 6 Mean", "EDA MFCC 6

		<p>Median"]; ["EDA MFCC 12 Mean", "EDA MFCC 12 Median"]; ["EDA MFCC 7 Mean", "EDA MFCC 7 Median"]; ["EDA MFCC 0 Mean", "EDA MFCC 0 Median"]; ["EDA MFCC 4 Mean", "EDA MFCC 4 Median"]; ["EDA MFCC 1 Mean", "EDA MFCC 1 Median"]; ["EDA MFCC 11 Mean", "EDA MFCC 11 Median"]; ["EDA MFCC 8 Mean", "EDA MFCC 8 Median"]; ["EDA MFCC 10 Mean", "EDA MFCC 10 Median"]; ["EDA MFCC 9 Mean", "EDA MFCC 9 Median"]; ["EDA Mean", "EDA Power", "EDA Tonic Max", "EDA Tonic Mean"]; ["EDA PSD Max", "EDA PSD Mean", "EDA PSD Std"]; ["HRV SDNN1", "HRV SDNN2"]; ["EDA SCR Area Under Curve", "EDA SCR Mean"]; ["EDA Std", "EDA Tonic Std"]; ["HRV CVNN", "HRV CVSD"]; ["Accelerometer Non-linear energy", "Accelerometer Std", "Accelerometer Tremors"]; ["Accelerometer FFT Std Energy", "Accelerometer Peak Power"]; ["HRV IALS", "HRV PIP"]; ["EDA Phasic Min", "EDA Phasic Std"]; ["HRV pNN20", "HRV pNN50"]</p>
High Kendall correlation (≥ 0.98)	25	<p>["EDA MFCC 4 Mean", "EDA MFCC 4 Median"]; ["EDA Wavelet 0 Energy", "EDA Wavelet 0 RMS"]; ["HRV CSI", "HRV SD1SD2"]; ["EDA MFCC 3 Mean", "EDA MFCC 3 Median"]; ["HRV Power HF", "HRV Power log HF"]; ["HRV RMSSD", "HRV SD1", "HRV SDSD"]; ["HRV CVI", "HRV S", "HRV SDNN"]; ["EDA Wavelet 1 Energy", "EDA Wavelet 1 RMS"]; ["EDA Wavelet 2 Energy", "EDA Wavelet 2 RMS"]; ["EDA Wavelet 3 Energy", "EDA Wavelet 3 RMS"]; ["EDA Wavelet 4 Energy", "EDA Wavelet 4 RMS"]; ["HRV C1a", "HRV C1d"]; ["EDA MFCC 8 Mean", "EDA MFCC 8 Median"]; ["EDA MFCC 5 Mean", "EDA MFCC 5 Median"]; ["EDA MFCC 9 Mean", "EDA MFCC 9 Median"]; ["EDA MFCC 2 Mean", "EDA MFCC 2 Median"]; ["EDA MFCC 0 Mean", "EDA MFCC 0 Median"]; ["EDA MFCC 1 Mean", "EDA MFCC 1 Median"]; ["EDA MFCC 12 Mean", "EDA MFCC 12 Median"]; ["EDA MFCC 11 Mean", "EDA MFCC 11 Median"]; ["EDA MFCC 7 Mean", "EDA MFCC 7 Median"]; ["EDA MFCC 10 Mean", "EDA MFCC 10 Median"]; ["EDA MFCC 6 Mean", "EDA MFCC 6 Median"]; ["EDA Mean", "EDA Tonic Mean"]; ["EDA PSD Max", "EDA PSD Std"]</p>

Figure S1. Explained variance ratio graphic.



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DISCUSSION

Overall Discussion of the 4 studies of the PhD project

Reminder of objectives

The main objective was to determine the role of craving in the development of SUD and its severity, its impact on long-term outcomes after initial exposure to treatment and its physiological correlates.

We had 4 *major hypotheses*:

- (1) Craving is a central criterion in DSM-5 SUD network across all substance users;
- (2) The presence of craving is associated with more severity (symptom count) and more use (quantity/frequency).
- (3) A better response of craving to treatment at initiation of treatment (i.e.: a more rapid decrease of craving at the beginning of treatment) is associated with a higher probability for remission at long-term;
- (4) craving is associated with a pattern of physiological changes in daily life from cardiac, electrodermal, accelerometer and skin temperature signals.

To meet our objectives and address our hypothesis we studied craving as a diagnostic criterion (a trait) and a dynamic phenomenon (a state) in two sets (Part I and II) of two studies each (total of 4 studies, considered as 4 individual experiments).

PART I: Explore craving as a diagnostic criterion (trait), first by studying its place and relationship within DSM-5 SUD criteria and by examining its role in the development of SUD.

PART II: Exploring craving as a dynamic phenomenon (state), first by studying the impact of early responses of craving to treatment on long-term outcomes and by investigating its physiological markers in daily life.

Putting results into perspective

Craving: role in DSM-5 SUD network and in the SUD development

We found that **craving was the most central diagnostic criteria across the 11 SUD criteria for five substances networks** (*Manuscript 1*), confirming our hypothesis. Our results highlight the role of craving in SUD as a criterion that could influence the entire network and play a major role in the disorder across five substances (alcohol, tobacco, cannabis, opiate, cocaine) and suggests that some criteria may not contribute to the construction of SUD, such as criteria related to consequences, as already shown by previous studies (Shmulewitz, Keyes et al. 2011, Chung, Martin et al. 2012, Kervran, Shmulewitz et al. 2020). Interestingly, craving appears to be stable in its central position in the network, independent of substance type, compared to other criteria such as those related to consequences. Our study was the first network analysis of the full 11 DSM-5 SUD diagnostic criteria. These results strongly suggest that craving could be a core symptom of SUD, and a fundamental target to understand and modify the network in terms of occurrence (Bringmann, Elmer et al. 2019, Hallquist, Wright et al. 2019). Hence, we have conducted a study in a sample of users not in treatment (*Manuscript 2*) suggesting that craving could acts as a driver symptom leading, by its stable roots over time, to the development of SUD, notably trough continued use of reinforcing substances. We founded that the **presence of craving at baseline and over time by its endorsement frequency was associated with greater severity** for alcohol and tobacco users, **and greater frequency of use** for alcohol users. According to craving status (yes/no) at baseline, the number of SUD criteria endorsed was significantly different at baseline but not at 12 months, suggesting that craving could be a differentiating marker of SUD severity or development but that our samples were too severe to observe the early value of craving. Moreover, our results show that participants who always reported craving had greater severity compared to those that never reported craving, and that those that reported craving sometimes were in-between for severity. **These results suggest a dose-dependent response relationship between “dose” of craving (always, sometimes, never) and severity and use days “response” (number of SUD symptoms and number of days use)**. Our findings suggest that the more time goes by, the more craving becomes entrenched, and the more this will lead to the development of other criteria with a dose-response effect, which is in line with our hypothesis that craving could be one of the first

symptoms of addiction to appear. This is in line with other studies (DiFranza, Rigotti et al. 2000, de Bruijn, van den Brink et al. 2005, Gervais, O'Loughlin et al. 2006, Morgenstern, DiFranza et al. 2016), making it a potential etiological symptom of SUD. To explore the direction of these associations we used hierarchical linear modeling which showed that craving at one-moment was associated with increased SUD criteria at the same moment, but not for the next-moment (3 months after). However, craving at one-moment was significantly associated to increased frequency of use at the same moment and at the next-moment. This positive association was already shown in daily life settings across substances especially in the following hours (Serre, Fatseas et al. 2015, Panlilio, Stull et al. 2019, Cavicchioli, Vassena et al. 2020, Burgess-Hull, Panlilio et al. 2022, Ellis, Mun et al. 2022, Vafaie and Kober 2022). Our results provide an additional element, confirming that craving is a trigger for use even 3-months later and could act as a driver symptom leading, by its persistence over time, to the development of SUD and its severity.

Influence of craving changes on long-term relapse and physiologic correlates in daily-life

We found that **patients in relapse after 5 years or more in treatment had a reduced craving intensity change during the first two-weeks of treatment, 5 years previously, compared to patients that were abstinent and whose craving had decreased more** (*Manuscript 3*). These results were in line with our hypothesis which was that a better response of craving to treatment at initiation of treatment (i.e.: a more rapid decrease of craving at the beginning of treatment) would be a marker of long-term treatment response. Other studies have explored the trajectory of craving or withdrawal after cessation of use that appeared to be highly predictive of subsequent short-term relapse (one year or less) (Piasecki, Jorenby et al. 2003, McCarthy, Piasecki et al. 2006, Piper, Federmen et al. 2008, Piper, Schlam et al. 2011, Shiyko, Lanza et al. 2012). Our study is the first to demonstrate that the early response of craving during the first two-weeks of treatment, captured in daily-life by EMA, could persist overtime and would be predictive of long-term outcome after 5 years or more. Moreover, we founded that **a lower craving inertia was observed at treatment initiation among the relapse group**. This result suggests that, for participants with poorer long-term outcome, craving intensity exhibited a slower decrease over the first two-weeks of treatment, and was more variable from one moment to the next. The lower craving inertia (higher moment to moment craving variability) may translate the persistence of craving reactivity to cues and other everyday life triggers, which was not the case for the participants in the remission group, and for which craving was more stable from moment to moment, possibly less influenced by cues and everyday life triggers due to the treatment interventions (psychotherapy and pharmacotherapy), and consequently their craving decreased more over the same 14-day period of treatment aiming at reducing craving, cue exposure and substance use. Finally, our finding should be interpreted with caution due to the limited sample size, and the study findings need to be replicated in other settings. To go a step further, we need to ask whether craving is a major factor contributing to the persistence and chronicity of the disorder, either by itself, or in interaction with other contributors such as cues. We have developed a generalizable method to detect craving and its physiologic correlates across substances in daily-life with the combination of EMA and wearable sensors, by using machine

learning algorithm (*Manuscript 4*). **Our results showed our models of classification were able to classify episodes of craving vs. no-craving with a better cross-validated accuracy than a random binary classifier** (Müller-Putz, Scherer et al. 2008, Nahm 2022). This is an important breakthrough in the underlying neurobiological mechanisms of craving, since it suggests that it is possible to physiologically identify craving in everyday life. By overcoming limitations of previous studies (Kennedy, Epstein et al. 2015, Chatterjee, Hovsepian et al. 2016, Carreiro, Chinthia et al. 2020, van Lier, Noordzij et al. 2022), our study provides new information on the **physiological features most involved in the identification of craving, namely those related to electrodermal activity and heart rate variability**. Based on these measurements indicating an elevated arousal even in measures reflecting the basal state (tonic component of EDA) and at the same time a peak activity (phasic component of EDA) during craving conditions, we hypothesize that craving maybe related to poor activation of the autonomic system at rest, i.e., a basal elevation of certain parameters such as HR and EDA and a high arousal at rest. This basal level, which is already high in individuals, could increase during craving episode, making it possible to distinguish it from no-craving episodes, but suggesting that for people with addiction, the periods without craving may not be without abnormalities. **This set of features forms a physiological pattern, which we called *the autonomous craving signature (ACS)*, that distinguishes craving from no-craving states**. The fact of having identified a pattern of physiological parameters provides important information on the physiological nature of craving and paves the way for the development of biomarkers and their use in everyday life.

Limits to be considered

Self-reported data

An important concern in collecting self-report measures is ensuring the accuracy and validity of data. Whether intentional or not, participant can adjust their responses based on perceived social norms to avoid embarrassment, discrimination or other consequences, which can introduce bias in responses such as leading substance users to conceal certain types of consumption (e.g., (Reichert, Gan et al. 2021)). However, a number of precautions have been taken to avoid this. First, to help mitigate the effect of socially desirable responding bias, research has identified several methods that we used such as the ensuring participants of their anonymity and confidentiality of responses (Paulhus 1991). In addition, self-reported substance use tends to be accurate in the absence of sanctions (Magura, Goldsmith et al. 1987), thus, we assured participants that the answers would not be shared with care staff, and would not influence their care. Finally, consumption was objectively monitored by means of urinary toxicity, alcohol and carbon monoxide measurement. A previous study had confirmed the validity of self-reported consumption data compared with urine assays in the same population (Denis, Fatséas et al. 2012).

Craving assessment

In part I studies, craving was considered as a trait (presence or absence) and evaluated as a diagnostic criterion according to the DSM-5, defined as *“Craving or urge, strong desire or urge to use”* (American Psychiatric Association 2013, Hasin, O’Brien et al. 2013). However, it is possible that people with less insight do not consider their cravings as craving. This is because, in theory, assigning the qualifiers "irrepressible" or "obsessive" requires good judgment of one's own experiences, which is not the case when insight is low (Vohs, George et al. 2016, Thirioux, Harika-Germaneau et al. 2020).

In part II studies, craving was considered as a state (variable intensity) and was evaluated with EMA with the question *“Since the last questionnaire, have you felt a desire to use [main addiction]?”* by a numeric scale of 7 points (from 1 (no desire) to 7 (extreme desire). This type of scale has shown good sensitivity to rapid fluctuations in psychological states (e.g.,

(Serre, Fatseas et al. 2015, Enkema, Hallgren et al. 2020, Cleveland, Knapp et al. 2021). In EMA, the term "craving" has been replaced by "desire" ("envie" in French), partly to avoid the need to identify craving as "intense or obsessive", and partly because the word "craving" is little used in everyday French and could lead to difficulties in understanding and under-assessment of this phenomenon. However, this single-item assessment did not take into account the multidimensional aspect of craving (e.g., automatic, interoceptive or obsessive), and the reliability of such a measure is debatable (Sayette, Shiffman et al. 2000). However, the choice of this single item was justified by the need for a simple and rapid measure, applicable to all addictions, and which could be integrated into questionnaires of short duration and repeated over time. In fact, it seems to be better suited to predicting daily use than multidimensional scales (Enkema, Hallgren et al. 2020, Vafaie and Kober 2022). To ensure good craving collection, the level of clinical insight was assessed prior inclusion.

Assessment periods and population studied

We studied two populations at different stages of their addiction: users not in treatment and not seeking treatment vs. users not in treatment, but seeking treatment vs. users in treatment. A total of 1,528 subjects participated in the 4 studies. 1,398 subjects were recruited from ongoing or previous research cohorts, and 130 subjects were newly recruited. All participants had documented informed consent.

Participants included in the ADDICTAQUI cohort and the BIOEMA – CSAPA study were all voluntarily attempting to control their use. The studies began at the initiation of treatment, generally corresponding to the start of the attempt to control use, but complete abstinence was not a prerequisite for treatment. As a return to controlled use or a significant reduction in use also leads to an improvement in the patient's prognosis, it is now also considered a positive outcome of treatment (Witkiewitz, Kranzler et al. 2021). The choice of this period at the start of treatment was justified by the need to find a period when craving and episodes of use would be reported with sufficient frequency, especially as they diminish with time in treatment (Fatseas, Serre et al. 2015, Cleveland, Knapp et al. 2021).

Participants included in the ECEDA study and the BIOEMA – GENERAL POPULATION were all users of at least one substance (tobacco, alcohol or cannabis) and had no intention of reducing or controlling their use, or seek treatment. We chose to study this population to increase the variability of the level of addiction and to have access to population of users which should present either no SUD, or a mild or moderate SUD compared to treatment population with an over representation of severe SUD. However, there was a difference between these 2 samples from general population. While participants in the BIOEMA – GENERAL POPULATION (*Manuscript 4*), were recruited by campaigns in the general population (billboards, social networks...), the recruitment of participants for ECEDA study (*Manuscript 2*), was via the KANOPEE app that is a smartphone app developed to screen and prevent the use of substance and its complications (Auriacombe, Fournet et al. 2021). Even if participants were not treatment seeking, they represented a population concerned about their use, which could constitute a bias by targeting only a part of the general population concerned with identifying possible addiction problems.

Analyses of BIOEMA study has been performed among all participants (CSAPA and GENERAL POPULATION) (*Manuscript 4*). It cannot be ruled out that some of our results may differ from one population to another. Analyses in separate samples, once sufficient numbers have been reached, will enable us to verify this point.

Assessment strategy in everyday life

Two studies in this PhD were carried out in everyday life. The ESM study (*Manuscript 3*) used signal-contingent as assessment strategy, while the BIOEMA study (*Manuscript 4*) used both signal- and event-contingent. The signal-contingent assessment strategy is time-based, i.e., assessments are automatically and randomly presented according to a frequency defined in advance by the application, while the event-contingent assessment strategy is event-based, i.e., initiated by the subject himself when the event occurs. Measures of protocol compliance in EMA studies related to time-based assessment is typically reported as the percentage of prompts “answered” out of those issued and research reported signal-contingent compliance rates between 65% – 92% for addiction population (Schüz, Walters et al. 2014). The compliance in our 2 studies was correct with 79.9% in *Manuscript 3* and 85.8% for *Manuscript*

4. Compliance related to event-based assessment is more problematic to calculate, as we do not know how many times an event (e.g., craving) has actually occurred. Using alternative measures, studies have compared the number of cigarettes recorded to the overall number of cigarettes per day reported by participants, suggesting that participants report only around 60% of the cigarettes they smoke (Schüz, Walters et al. 2014). It is therefore possible that the number of craving events is underestimated. However, the use of these 2 methods in the assessment strategy was for several reasons. First, to identify physiological changes associated with craving, the fact to have both signal- and event-contingent to assess craving allows us to ensure the identification of craving through 2 assessments (event- and signal-contingent) (*Manuscript 4*). Thus, this double-check enabled us to suggest that the changes observed were due solely to craving, and not to confounding factors. With this strategy, the hypothesis of the impact on our results of an under- or over-estimation of craving events is reduced. Thus, the choice of a strategy based on both time and event seemed more relevant to us and enabled us to respond to our hypotheses.

OVERALL PERSPECTIVE

This PhD project highlights the role of craving that leads to the development and maintenance of addiction, and that consequence-related criteria are only the consequence of excessive unregulated use due to loss of control over use. Thus, it calls into question the relevance of consequence criteria for the diagnosis of addiction (Martin, Langenbucher et al. 2014) and the possibility for them to be removed in future revisions of DSM. Currently most individuals with an addiction are screened and identified more often by the consequential criteria, and treatment interventions are frequently focused on these same criteria. However, these results suggest that these consequence criteria do not contribute to the mechanisms of SUD but may be secondary to the exposure to pharmacological properties and toxicity of individual substances (O'Brien 2017). This suggestion applies across all substances, which may call into question the usefulness of separating research in terms of substance types or behaviors. It reinforces the hypothesis that craving is transdiagnostic, being an underlying mechanism of addiction that may exist independently of the substance, unlike the consequences related criteria (O'Brien 2017). This hypothesis of homogeneity of craving across SUDs is bolstered by neuroimaging meta-analysis showing that craving shared similar neural substrates across SUDs (Chase, Eickhoff et al. 2011, Kühn and Gallinat 2011). For example, a fMRI marker of craving has been reported across substances/food (Koban, Wager et al. 2023) and a transdiagnostic craving network was identified using connectome-based predictive modeling (CPM) applied to functional connectivity data (Kathleen A. Garrison, Rajita Sinha et al. 2023). Craving was already considered by many researchers and clinicians as a transdiagnostic and a major treatment target to reduce relapse frequency (O'Brien 2005 a, Auriacombe, Serre et al. 2018), regardless of substance type (Vafaie and Kober 2022). Moreover, some authors consider that addiction or use disorders refer not only to substances, but potentially to all reinforcing objects or behaviors, prompting us to explore the network of symptoms specific to reinforcing behaviors. Of notice, a recent study showed the validity of a potential food use disorder (FUD) derived from the DSM-5 SUD criteria (Chapron, Kervran et al. 2023) that could be used to explore FUD criteria and their interaction in term of network. Thus, it would be interesting to explore use disorders regardless of the object (substance or behavior), and specifically in symptom networks devoted to reinforcing behaviors (eating, video games, gambling...).

On another note, the study on SUD diagnostic criteria network (*Manuscript 1*) was conducted in a sample of addiction treatment seeking adults and those had a severe SUD: this characteristic of our population reinforces our results, since even in a severe population, which could present more consequences criteria, these criteria remain peripheral in the network, while the craving criterion remains a central criterion. It would then be interesting to study the DSM-5 SUD symptom network in a different population, such as regular users in the general population, in order to explore the position of the criteria and their interaction in the network in a less severe population. This would make it possible to explore, among the criteria for loss of control, whether craving is still central, in line with our hypothesis of its early appearance in the disorder.

In this perspective, our second study (*Manuscript 2*) suggested that craving could acts as a driver symptom leading, by its stable roots over time, to the development of SUD. This project supported our hypothesis that craving could be an early predictive marker of addiction development and severity. This role of craving has been suggested in several studies (Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2015, Kervran, Shmulewitz et al. 2020), especially in one meta-analysis confirming its causative role in use and relapse (Vafaie and Kober 2022), and in longitudinal studies (DiFranza, Rigotti et al. 2000, de Bruijn, van den Brink et al. 2005, Gervais, O'Loughlin et al. 2006, Morgenstern, DiFranza et al. 2016, Fink, Shmulewitz et al. 2022) making it a potential etiologic marker of addiction. Furthermore, the dose-response relationship suggesting that the persistent presence of craving over time is associated with more severity, further strengthening our hypothesis. However, as our analyses focused solely on the diagnostic criteria for alcohol (AUD) and tobacco (TUD), it cannot be ruled out that different results could be found with other substances or reinforcing behaviors and with a longer time window. It would be important, in future studies, to explore the possibility of replicating these results both for other substances or behaviors, and in longitudinal studies that take a longer time frame. The clinical implications are significant and open up new prospects for intervention. We already knew that craving was predictive of use (Fatseas, Serre et al. 2015, Serre, Fatseas et al. 2015, Vafaie and Kober 2022), but our results (*Manuscript 1 & 2*) tend to show that craving could be, beyond use, a driving symptom of addiction leading to the onset of SUD. We suggest that the mere presence of craving could already be a warning sign underlie a transition to a loss of control over use, and thus the evolution to addiction. Thirteen percent

of the adult population have mild to moderate SUD (i.e., 2-5 symptoms) (Hughes, Helzer et al. 2006) and only a few will progress to severe SUD (Swendsen and Le Moal 2011), giving us a window of opportunity to intervene before the occurrence of the consequences criteria, thus be a target for prevention to reducing the burden of addiction. The early stage of addiction has been called *Preaddiction* (McLellan, Koob et al. 2022) and we suggest that craving could constitute a screening target within the pre-addiction framework. Thus, the only presence of craving may be prognostic and etiologic of SUD development.

This PhD project highlight that craving plays a role in the chronicity of SUD and that it could be identified by a physiological biomarker. Indeed, several studies have shown the role of craving as a proximal factor (Serre, Fatseas et al. 2015, Auriacombe, Serre et al. 2018, Serre, Fatseas et al. 2018, Cavicchioli, Vassena et al. 2020, Vafaie and Kober 2022), but our study is the first to demonstrate its impact on long-term outcomes and thus, the role of craving as a distal factor of relapse, i.e., a factor that could make the individual more vulnerable to relapse (Witkiewitz and Marlatt 2004). Our findings open the way to explore changes in craving at the start of treatment to anticipate individuals more vulnerable to relapse on the long run to prevent SUD severity progression. Elsewhere, it would be interesting to explore other trajectories such as high- or low-craving groups or more complex patterns (Burgess-Hull, Panlilio et al. 2022), to explore whether some of them are more associated with long-term outcomes. In term of clinical perspectives, the assessment of individual trajectories of craving could lead to personalized monitoring for better relapse prevention. For example, mobile technologies, such as smartphone apps, could offer accessible, easy-to-use, and autonomous measures of symptoms dynamics in daily life (Dulin and Gonzalez 2017, Bahadoor, Alexandre et al. 2021), that could be used to detect the most appropriate moments to propose interventions (Nahum-Shani, Smith et al. 2018, Serre, Moriceau et al. 2023).

Our results, and that of others (Kennedy, Epstein et al. 2015, Carreiro, Chintha et al. 2020) exploring the physiological correlates of craving provide clues as to the autonomous activity involved in craving. However, although our marker is cross-validated for internal validity (Pal and Patel 2020), future studies should explore the external validity of this pattern to generalize its predictions to new data not used during training (Findley, Kikuta et al. 2021). This would

enable the development of a universal pattern of craving. The fMRI neuromarker of craving (i.e., NCS) (Koban, Wager et al. 2023) is a real breakthrough in craving biomarkers. However, fMRI protocols are not directly accessible in daily life making it difficult to identify this pattern to prevent relapse in users in treatment, compared to ACS that is accessible through daily life generated data. Moreover, the NCS was identified from cue-reactivity protocols which may not have been representative of cues-induced craving in everyday life for all individual. It could be interesting to explore, in future investigation, whether the NCS predicts other correlates of craving such as psychophysiological responses of craving as suggested by authors (Koban, Wager et al. 2023), that we proposed to be the ACS. The concomitance and discovery of a marker that tracks both brain activity via fMRI and autonomous activity via wearable sensors would enable the development of a reliable and valid biomarker of craving, both in everyday life and in the laboratory. Elsewhere, the pattern we identified in daily life is a pattern based on craving with an intensity equal to or greater than the average of the EMA measurement scale and predictive or not of use in the following hours. However, previous studies showed that it is not the absolute value of craving (presence or absence) that predicts use but the variations of craving which predicts the increasing likelihood of use. Thus, it would be interesting to go further, by studying whether our pattern could be different from craving predictive of use rather than the pattern of craving. Studying the pattern associated with craving as a predictor of use would enable us to identify "at-risk" craving episodes.

In a clinical perspective, the ACS could have a direct clinical impact on use and relapse. The passive identification of craving would be particularly important, especially in individuals who have difficulty identifying craving (Cavicchioli, Vassena et al. 2020, Raftery, Kelly et al. 2020, Lambert, Serre et al. 2021). Indeed, this pattern could be used in daily life to identify the appearance of craving in real time and allow immediate intervention. The development of protocols of daily-life craving regulation that could constitute in the future a warning system that would be activated when this pattern is present both to warn the user, to promote a better insight and to allow a relay towards care if needed or towards a Just-in-Time Adaptive Interventions (JITAI) (Serre, Moriceau et al. 2023). JITAI adapt over time to an individual's changing status and are designed to offer suitable intervention strategies based on real-time, real-world context (Nahum-Shani, Hekler et al. 2015). Thus, it could be studied in the context of future investigations, the integration of JITAI which would be triggered by the identification

of the ACS via real-time monitoring. these interventions could be based on mindfulness meditation techniques (Garland, Gullapalli et al. 2023) or even on the implementation of wearable biofeedback techniques (ter Harmsel, Noordzij et al. 2021).

CONCLUSION

The aim of this PhD project was to determine the role of craving in the development of SUD, its impact on long-term outcomes and its physiological correlates. By studying craving as a trait, we showed that **craving was the most central criterion across the 11-SUD diagnostic criteria for five substances networks**. Longitudinally, the exploration of diagnostic criteria in users not in treatment, from general population, demonstrated that the presence of **craving at baseline and over time by its endorsement frequency** (Always, Sometimes, Never) **was associated with greater severity and frequency of use** in the sense of a dose-dependent response relationship. By studying craving as a fluctuating state, we showed that **craving intensity decrease** during the first two-weeks of treatment **was slower for participants not abstinent 5 years later**. Finally, we found **physiological correlates associated with craving in daily-life**, composed by a pattern which we labeled the **Autonomic Craving Signature (ACS)**. Taken together, these set of 4 studies underline the central role of craving, the need to better understand it's the underlying mechanisms due to its role in the development of addiction.

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Appendix 1. Commentary (in submission) on the preventable deaths related to substance use.

Making alcohol and tobacco preventable deaths really preventable! Addiction as a modifiable risk factor for alcohol and tobacco preventable mortality.

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The association between use of alcohol and tobacco, and negative health consequences, increased morbidity and mortality is well documented.¹ Negative health consequences have been linked to toxic characteristics of these substances. As users are voluntarily exposing themselves to these substances, and consequently to their toxicity, it has long been, and still is, suggested that such consequences should be “preventable” by simply reducing or suspending self-exposure to such toxic substances.² Their use are among the first lead of “preventable/avoidable” deaths and morbidity worldwide. Indeed, prevention interventions are based on dissemination of information about the negative consequences of use on health, and encouragement to reduce or avoid use, through making access more difficult (for example by increased cost for the user through taxation or by making use illegal). In this perspective, these substances are the focus of public health campaigns in many countries, that promote cessation or reduction of use, such as “Stoptober” for tobacco, or “Dry January” for alcohol. Despite some effectiveness, the prevalence of use remains important.³

Although any level of use of alcohol and tobacco is associated with higher risks of negative consequences, these toxic effects and adverse health consequences nonetheless increase with quantity/frequency of use. Quantity of tobacco use is strongly associated with lung cancer with a relative risk of 22.4 for light smokers and up to 50 for heavy smokers.⁴ For cancer of the esophagus, most frequently associated to alcohol use, drinking from small to moderate and high quantities significantly increases the risks of this cancer.⁵ Thus, people who are the most at risk of substance-induced morbidity/mortality are those who use the most and are also likely to benefit the most from reducing use or abstaining.

Unfortunately, these substances also have important reinforcing properties that promotes repeated use, and the risk of developing a substance use disorder (SUD). SUD, or addiction, is considered a chronic condition characterized by loss of control over use which translates as an impaired ability to modulate use to rational choices (for example based on knowledge of toxic effects), even when experiencing negative consequences of use.⁶ Consequently, individuals with addiction will use larger quantities and more frequently over time, which in turn will make them more at risk of developing toxic consequences and complications. Indeed, there is a higher proportion of cancers among populations with SUD than without SUD.⁷ Furthermore, epidemiological data show that a significant proportion of

tobacco and alcohol regular users already have a SUD (up to 67.5% and 26.6%, respectively)⁸ and this will be before having time for consequences to occur.

Consequently, tobacco and alcohol regular users will be among the most in need of interventions to prevent negative health outcomes of use, however, for those with SUD, cancers and health damages due to substance use will not be easily preventable, because of their impaired ability to modulate their use, despite knowledge of risk, experience of morbidity, and/or willingness to abstain. In this population, the usual prevention messages promoting reduced use or abstinence, could be more difficult to be followed, making them eventually deleterious. Indeed, such encouragements to reduce substance use to stay healthy, and prevent the development of diseases associated with morbidity and mortality, may expose them to repeated failures, increased guilt for not being able to reduce use or achieve abstinence, reduced self-esteem and self-efficacy, and contribute to stigmatization. Stigma against SUDs, including self-stigma, has been shown to contribute to continued use, reduced access to treatment services, and decreased opportunities for remission from SUDs.⁹

Addiction may thus be considered as a major risk factor for continued use despite access to information and encouragement to reduce use, and this risk factor is modifiable. When SUD is properly identified, SUD treatments are effective and present comparable efficacy with treatments of other chronic conditions.⁹ This calls for a major shift in cancer prevention campaigns worldwide. Encouragement to limit use of substances with toxic effects should be contingent to awareness campaign about SUD, promotion of SUD screening, and easy access to SUD treatments, including at the early stage of addiction.¹⁰ Instead of: “Want to avoid cancer: reduce or stop alcohol and tobacco”. We may have a better public health impact with: “Want to avoid cancer: Come and screen for SUD.”

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