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Investigating Autobiographical Memory Impairments in Chronic Heavy Cannabis Users: Methodology and Hypotheses

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Introduction

Cannabis is the most consumed illicit substance in industrialized countries, and the French count among the highest users in Europe [1]. Chronic heavy cannabis use (CHCU) is usually associated with a deficit of executive functions [2] together with impaired working memory [3], and both these systems are involved in various memory processes, including autobiographical memory (AM) [4]. AM is defined as a set of personal general knowledge and memories of highly specific episodes that an individual accumulates throughout their life. AM is inherent to the construction of self and personal identity, and gives a sense of continuity of the self across time [5]. The model the most widely used to explain AM running is that of Conway and Pleydell-Pearce [6].

These authors constructed a dynamic hierarchical model incorporating three levels:

- Periods of life, which are long segments of life measured in years or decades, and compounds of the goals, plans and themes, referring to a particular period.
- General events consist of episodes related to a theme and repeated events and / or events which last more than one day. According to the author, it would be the natural input mode AM and thus the most common.
- Detailed specific events or specific details, it's the least abstract level. These details concern the phenomenological register and are measured in hours, minutes or even seconds.

Note that the recovery process is managed through the action of the central administrator, dependent of frontal lobes action, heavily involved in operations of executive functions.

The AM system allows individuals to mentally travel in subjective time to re-experience past personal events or pre-experience personal future events. As previously reported, these personal-specific events are of short duration (minutes or hours). Events are considered as episodic memories if they have a single source and are localized in place and time. AM allows the conscious recollection of specific personal events with numerous perceptual, contextual or emotional details. These details give an event its uniqueness and allow individuals to distinguish between real autobiographical events and imagined ones [6]. To our knowledge, few studies have tackled the links between AM and cannabis use. Relevant papers have highlighted a specific overgeneralization in AM [7] and an enhanced extinction memory recall "by preventing recovery of extinguished fear" [8]. The overgeneralization phenomenon is described by Conway and Pleydell-Pearce [6] as access to general event knowledge and self-referring knowledge where the generation phase of retrieval stops before the individual has constructed a detailed retrieval model. It can be compared to a disfacilitation of the retrieval process.

Williams et al. [9] described this overgeneralization phenomenon in depressed subjects through the involvement of three key elements, namely:

- The effect of capture preventing the specification of autobiographical events. The subject is fixed on the general memories recall and progression to the recollection of a specific memory is blocked. This is explained by the predominance of conceptual self-relevant representations during the early stages of memories recollection.
- A deficit in executive functions. In the model of Conway and Pleydell-Pearce, it appears that the Central Administrator has a key role in the recollection of autobiographical memories. It appears that the recall of general events requires minimal use of executive functions, contrary to recall specific details. An alteration of some executive functions such inhibition or update could increase the capture effect described above.
- Functional avoidance allows preventing or hindering the recall of emotions associated with memories. Indeed, the general memories recall tends to reduce the recollection of emotional material and thus allows the individual to avoid the consequences of an impact by this recall, especially when emotions associated with them are negative. This cognitive process could be considered as an adaptation strategy, especially an avoidance strategy [9].
- Note that this theorization of overgeneralization phenomenon is mainly based on the results obtained from subjects suffering from depressive disorders. However, it appears that this model could equally be appropriate among substance users and particularly to cannabis users.

In this sense, several research teams have highlighted an increasing number of general autobiographical events among alcohol dependent [10-12], opiates users [13-15] and cannabis users [16].

Regarding to animal model, several experiments have shown that CB1 receptor in knock-out mice fails to extinguish aversive memory. This impairment of extinction learning is found in various aversively motivated tasks, including the Barnes maze task [17], the light/dark box [18], and auditory fear-conditioning tests [19]. This result has been confirmed in studies using CB1 antagonist (Rimonabant) [17]. However, in contrast with the results in aversively-motivated tasks, the

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same study did not show significant results in experiments involving appetitive-motivated Barnes maze tasks [17].

On the same lines, a study by Rabinak et al. in humans found a similar pattern to animal studies: using a standard Pavlovian fear extinction paradigm and simultaneous skin conductance response measures, they showed that administration of oral dronabinol (synthetic THC) enhanced the extinction of recall [8].

Some researchers think that people with PTSD may be treated with cannabinoids. Indeed, the relationship between endocannabinoids, mnemonic processes and emotion suggests that the administration of cannabinoids could allow subjects to prevent the consolidation and untimely recall of traumatic memories [20]. In this sense, a recent review highlights the involvement of cannabinoids and glucocorticoids in the extinction of aversive memories [21]. Moreover, others information support these results. Regarding to animal studies, cannabinoid receptors in the amygdala and prefrontal cortex of rats could be involved in fear learning, consolidation, retrieval and extinction of memories associated with fear [22]. Indeed, a high level of endogenous cannabinoids (such as anandamide and arachidonoyl glycerol) in the basolateral amygdala complex could facilitate the extinction of aversive memory [19-22].

Chronic heavy cannabis use could impair AM processes through selective inhibitory effects on local inhibitory networks in the amygdala, as proposed by [19]. Moreover, some surveys show that the endocannabinoid system is considered as a regulating system of emotional responses ("regulatory buffer system") [23] and emotional-like behaviours [24]. The literature review of Ruehle et al. indicates a bidirectional influence of the endocannabinoid system on anxiety. It seems that the presence of low dose of agonist to the CB1 receptors induces anxiolytic effect whereas high doses cause anxiety. Concerning memory of fear, it also appears that the endocannabinoid system is involved in two opposing processes that are reconsolidation and extinction of aversive memories. These results suggest that the endocannabinoid system plays an important role in maintaining emotional homeostasis and influence the emotional regulation skills [23].

Although using different methods, studies on animal models [17-19] and the only study available in humans [7] both report an influence of endocannabinoid system on emotional memory processes, that is supported by neurophysiological data [21,22]. Regarding studies focusing on repercussions of regular cannabis use, note that users suffer from both cognitive [2,3,25-27] and emotional disturbances [28,29]. The current study proposes to analyse the link between emotional state of the participants, executive functioning and AM, because identified impairments of cognitive and emotional functioning could impact the future reconstruction of personal events as well as the recall of emotions associated with them. Here we present the hypothesis and methodology of an ongoing study designed to compare AM performances between CHCU and healthy controls.

The first key hypothesis is that chronic heavy cannabis use induces an overgeneralization of the autobiographical events recalled. The second key hypothesis is that specific autobiographical events recalled by cannabis users are less intense and more often positive than autobiographical events recalled by non-users shown in Figure 1.

If we confirm these two hypotheses, this could mean that the addictive process does not only depend on the positive reinforcement of the substance but also on the potential of sidelining autobiographical events that may disrupt the "self" of the subject. This attempt to avoidance may act as a consolidation process of addiction Figure 1.

Moreover, beyond the comparison of AM results of users and control subjects, we will :

- Measure the influence of substance use factors on outcomes to AM tools.

- Assess the relationship between cognitive performance and results to AM tools.

- Assess the relationship between mental state of the subjects and results to AM tools.

Materials and Methods

Participants

Due to the absence of references concerning the evaluation of AM in cannabis users by TEMPau in the literature, we are unable to accurately calculate the size of groups necessary for obtaining a sufficient strength test (0.80). Moreover, this test doesn't contain an unique score but several quotations by life periods. Regarding to the studies investigating cognitive disorders in cannabis users (between 10 to 44 subjects) [25-27,30-39] and regarding to a meta-analysis of works concerning overgeneralization of autobiographical events (between 12 to 37 subjects, excepted one study with 93 subjects in the experimental group but only 24 subjects in the control group) [40], we decided to include 30 cannabis users and 30 non-users subjects. Moreover, Potheegadoo et al. explore AM impairments in patients suffering from schizophrenia and they include 25 patients and 25 control subjects [41].

To be eligible for inclusion, participants had to be aged between 20 and 45 years old, have social security coverage, understand French, not suffer from any disorder on Axis I of DSM-IV-TR [42] (other than anxiety disorders and other than substance dependence/abuse for the "users" group), no history of neurological disorder, and not be under medication such as anxiolytics, anti-depressants or neuroleptics. Participants who are under guardianship or who have an IQ below 79 are not included. Female participants consuming more than 14 units of alcohol per week and male participants consuming more than 21 units per week are excluded. Subjects in the "users" group had to have consumed cannabis at least 10 times during the previous 30 days.

All groups are matched in terms of age, gender and level of education.

Procedure and tests

To perform all the assessments planned in the research protocol, we organize three evaluation sessions. In a first session, several tests are run to control non-inclusion criteria and participant comorbidities. During this session, several assessments of cognitive functions and emotional state are equally performed.

Mental disorders and premorbid intelligence

The MINI (Mini International Neuropsychiatric Interview) [43] explores the first Axis of the DSM-IV-TR in order to check for mental disorders. Premorbid IQ is estimated by the fNART (French version of the National Adult Reading Test) [44].

Substance use screening

Two separate scales are used to measure cannabis use level (CAST–Cannabis Abuse Screening Test) [45] and alcohol use level (French version of the AUDIT–Alcohol Use Disorders Identification Test) [46]. Tobacco dependency level is measured using the Fagerström test [47]. The protocol also includes a measure evaluating cannabis use motives (MMM – Marijuana Motives Measure) [48].

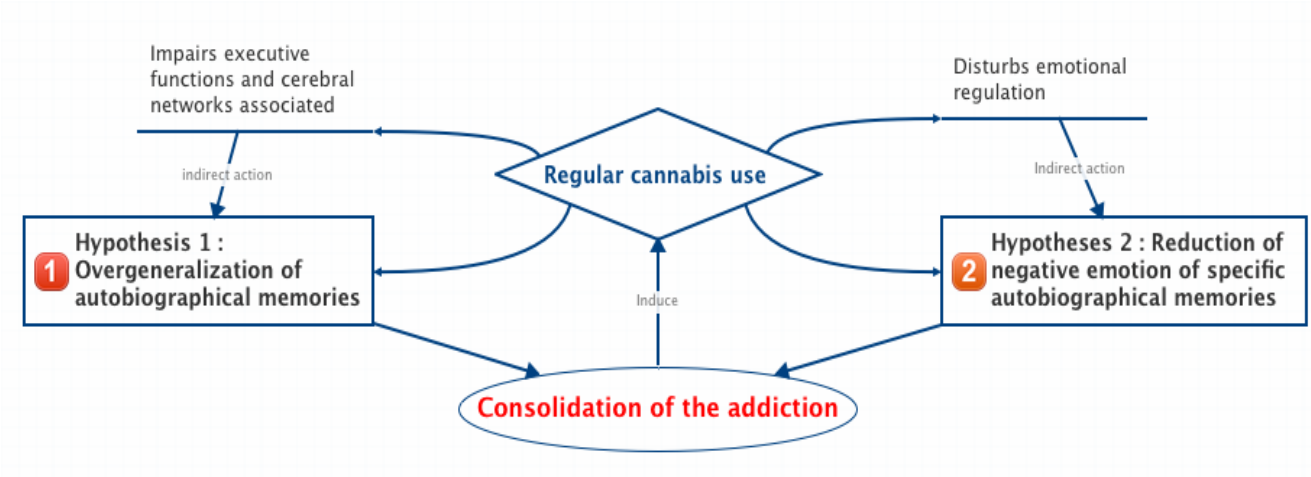


Figure 1: Graphical abstract of hypotheses.

Neuropsychological measures

Given the importance of the executive functions and working memory to reconstruct detailed specific autobiographical events, it is essential to measure the capacity of participants. Assessments are run on information processing speed (Code, WAIS III) [49], executive functions (Verbal fluency and TMT A and B) [50], working memory (Memory Span, WAIS-III) [49] and spatial memory (MEM III subtest) [51], which are known to be altered in CHCU and involved in AM.

Psychological measures

The study also explores the psychological state of participants using several scales. We assess anxiety (STAI-Y) [52] and depressive symptoms (MADRS) [53]. The level of stress (PSS-14) [54] is equally considered to make sure that a high level of stress during evaluation does not disturb the recall. Indeed, many unexpected events could possibly come to influence the recall for other stressful events. Furthermore, we evaluate the stress coping skills to see if, in this sample, users use more avoidance strategies (Brief COPE) [55]. In addition, these data will allow us to perform statistical analyses to evaluate the link between coping strategies and motivation to cannabis use.

Emotional regulation (DERS-F) [56] and alexithymia (TAS-20) [57] are equally assessed because several studies have shown that drug users have difficulties to manage their emotions [58], cannabis users being not spared [29]. Moreover, some authors notice that cannabis users would be more inclined to be alexithymic [7,28] and alexithymia could impair the emotional recall during autobiographical memories recollection. In the same way, these assessments will allow us to perform statistical analyses necessary to find relation between emotional valence and intensity scores and scores on emotional regulation and alexithymia scales. During the second and the third session, only the AM tests are carried out.

Autobiographical memory tasks

The episodic and semantic components of AM are explored through two ecological tests: the French 'TEMPau' test [59] and the French-version AVF (Autobiographical Verbal Fluency) test [59]. We have chosen these tools rather than AMT (Autobiographical Memory Test, Williams and Broadbent, 1986) [60], usually used to assess degree of autobiographical events specificity because the cues employed in the AMT (positive, negative and neutral) influence emotional valence of recalled memories. Which is essential given the second hypotheses, it's the neutrality of retrieval. These tools allow us to appreciate the amount of positive and negative memories.

We take as reference the study of Potheegadoo et al. 2012 and we choose to use an adapted version to the young population included in our study. Four life periods are assessed, instead of the 5 in the original test, covering the following intervals: childhood up to the age of 9, age 10 to 19, age 20 up to one year before the test, and the last 12 months [41].

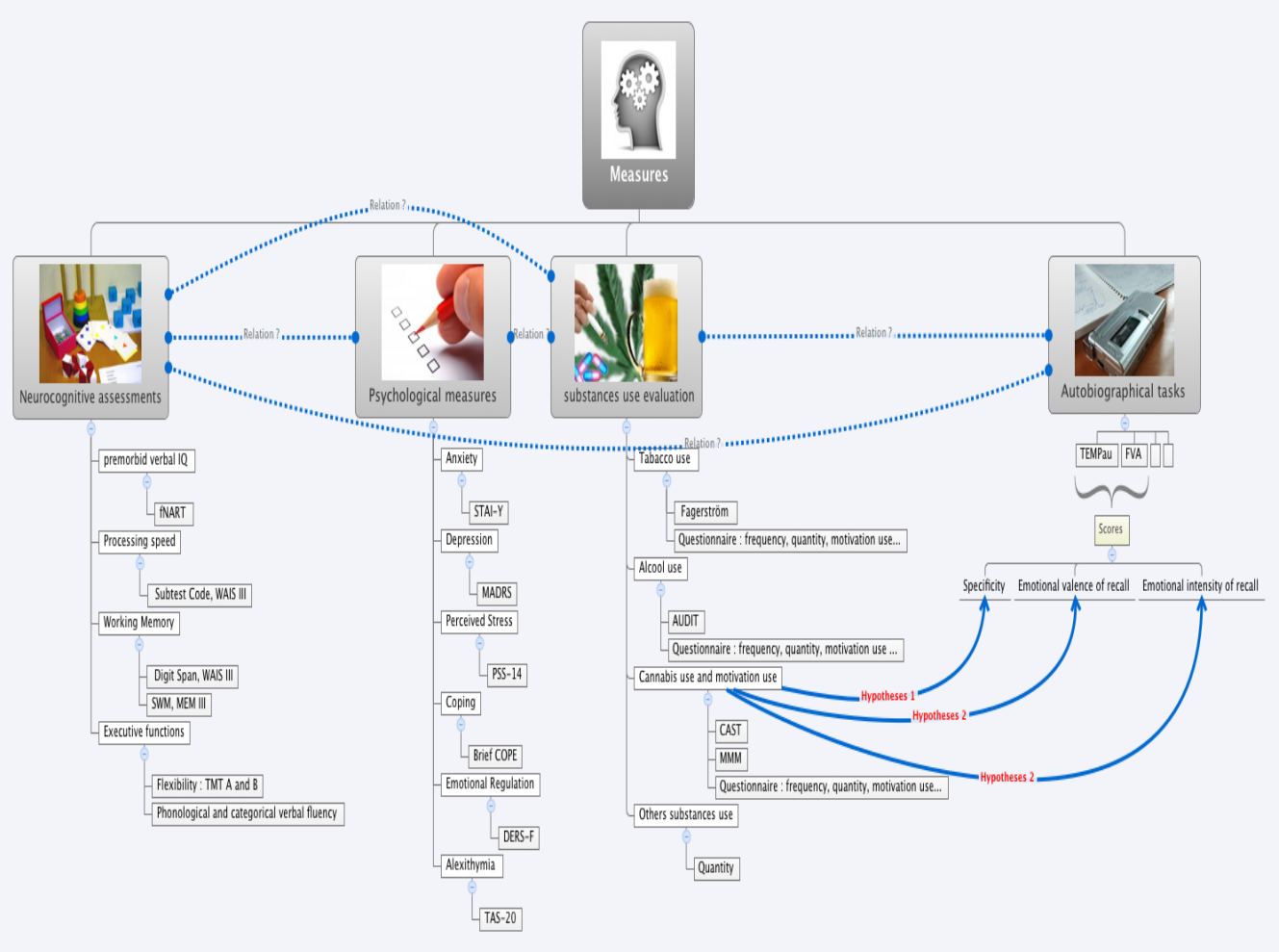
For TEMPau, the quotation of memories, recalled by participants, is estimated through several ratings, firstly calculated scores of all life periods (general score) and by life period (period score).

Mainly, an overall score of autobiographical events and a score of specific autobiographical events are calculated to answer to the hypothesis of overgeneralization of AM.

Visual perspective of participants during recall [61] is also considered. A Field perspective is assigned when the participant sees the scene through his own eyes, such as during the original event, and an Observer perspective is assigned when he sees himself in his memories from the point of view of an external observer. This measure is used to assess the memory specificity in terms of the semantization of AM. As episodic memory tends to become semantic with time and repetitions, Field perspective is preferentially assigned to specific memories and Observer perspective to generic memories.

Further, participants also estimate their consciousness during recall (R/K paradigm [62]). 'Remember' responses are given when participants are able to consciously and mentally re-live specific aspects of events. 'Know' responses are given when they simply knew an event had happened without any conscious recollection of it.

Otherwise, to answer to our second hypotheses, we choose to add an assessment of the emotional valence of AM and the emotional intensity with which the events are recalled to answer to our second hypothesis. For these two assessments, we use likert scales with 7 modalities range from -3 to +3. For emotional valence, the score -3 corresponds to very negative memories when recalled and the score +3 corresponds to very positive memories when recalled. For emotional intensity, the score -3 corresponds to memories whose emotion at the time of the recall is inexistent and the score +3 corresponds to memories whose emotion at the time of the recall is very intense.



fNART : French version of the National Adult Reading Test [44]; WAIS-III : Weschler Adult Intelligence Scale – 3rd Edition [49]; SWM, MEM-III : Spatial Working Memory, Echelle Clinique de Mémoire [51]; TMT A and B : Trail Making Test A and B [50], Verbal fluency [50]; STAI-Y : State and Trait Anxiety Inventory - Y [52]; MADRS : Montgomery Asberg Depression Rating Scale [53]; PSS-14 : Perceived Stress Scale – 14 items [54]; Brief COPE [55]; DERS-F : Difficulty in Emotion Regulation Scale – French version [56]; TAS-20 : Toronto Alexithymia Scale [57]; Fagerström [47]; AUDIT [46]; CAST [45]; MMM [48]; TEMPau : Test Episodique de Mémoire du Passé autobiographique [59]; AVF : Autobiographical Verbal Fluency [59]

Figure 2: Schematic representation of measures and tools.

For AVF, all scores are calculated in the same way as the quotation in the TEMPau, firstly, in general, then, by periods, but visual perspective isn't considered. Moreover, this task is composed to two parts; the one assesses personal semantic information and the other assesses the autobiographical retrieval [59]. Note that we have added the same assessment of emotional valence and intensity proposed in the TEMPau regarding to the autobiographical events recalled shown in (Figure 2)

Statistical analyses

First we will conduct a descriptive analysis of the collected parameters. Categorical variables are expressed as percentages and continuous variables as average, standard deviation, median, minimum and maximum.

Then we will perform a comparative analysis. We will use bivariate and multivariate linear regression models for the analysis of the main variables of judgment and we will use logistic regression models for secondary analysis.

The results to AM tests of the two groups will be compared with the software SAS by a bivariate analysis (depending on the nature of the endpoint, a Chi2 test or Pearson correlation test will be performed) and multivariate analysis where appropriate (depending on the nature of the endpoint, a model of linear or logistic regression will be applied). The alpha risk set at 5% for all statistical tests.

Discussion

The relationships between cannabis use and cognitive impairments [2,3,25-27] and between cognitive function and AM [4] converge to suggest that cannabis use could impact AM processes. Based on data from neuroimaging, studies on animals and the preliminary results on the impact of cannabinoids on memory recall in humans, we hypothesize that autobiographical events recalled by CHCU would lack specificity. We also assume that specific autobiographical memories would be less intense and less negative in CHCU than in non-users. This abstraction could protect individuals against certain phenomenological features related to personal experiences, i.e. emotions, feelings or visual imagery, that could threaten to disturb their emotional stability [63].

Even though the consensus is that cannabis addiction is linked to the effect of cannabinoids in the dopaminergic reward system [64], extinction of negative memory, as highlighted in animal studies [23], could also explain the cannabis dependence. Thus, if it is found that chronic heavy cannabis use leads to a deletion of negative AM that involves AM overgeneralization, the results could have major implications for therapy. This avoidance process could involve altered self-construction and self-perception. On clinical front, the attempt to reconstruct and integrate autobiographical events during psychotherapy sessions could become a new entry point in complex care for cannabis users. Sessions based on a CBT approach might enhance coping skills and emotional self-regulation in CHCU. On the theory front, we expect this methodology to (i) help better understand the overgeneralization phenomenon in cannabis users observed in the literature, and (ii) improve our understanding of the relationship between emotional regulation and cannabis use.

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