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MULTIDIMENSIONAL AND POPULATION-BASED GENETICO-EPIDEMIOLOGICAL RESEARCH IN AFRICA

FOCUS ON PSYCHOSIS, SUBSTANCE ABUSE AND TRAUMA

FACHMENTORAT

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"EVERYTHING SEEMS IMPOSSIBLE UNTIL IT IS DONE"

(Nelson Mandela)

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1. INTRODUCTION

Low-income countries, such as Ethiopia, have been underrepresented amongst participating sites in global psychiatric genetic collaborations. For example, the large published genome-wide association studies (GWAS) for schizophrenia, bipolar disorder, and major depression to date did not include samples from Africa and, overall, included only a small number of non-European samples or none at all *(Pardiñas et al., 2018)*. Recent efforts have focused on closing the gap between European-centered studies and those that utilize samples from other areas in the world, such as Asia, Middle-East, and Africa. Amongst other benefits, analyses in these samples hold the promise of allowing for a more in-depth insight into the biology underlying previously identified signals, e.g., allowing for fine-mapping of associations that take advantage of population-specific differences in linkage disequilibrium (LD) structure. Importantly, these samples will also help to identify new genomic regions that contribute to the etiology of psychiatric disorders *(McClellan et al., 2017)*. Finally, identification and exploration of environmental risk factors specific to low-income countries and population-specific genetic risk loci might help to shed light on the pathobiology and pathopsychology of psychiatric disorders in general and improve our understanding of the etiology and adequate therapy in non-European settings.

Recently, the potential role of environmental factors in the development of psychosis has been highlighted *(van Os et al., 2010)*. An environmental risk factor for psychosis unique to countries around the Horn of Africa is the chewing of khat (Catha edulis) leaves. Khat contains amphetamine-like alkaloids such as cathinone, cathine, and norephedrine, which have stimulating and euphorigenic effects on the central nervous system. In preparation of a future study on *khat abuse, trauma*, and *psychosis* in the Gilgel Gibe Field Research Center (GGFRC) in Ethiopia with a targeted sample size of 10,000 individuals, we have successfully conducted intertwined studies focusing on the assessment of phenotypes as well as environmental and genetic risk factors. We found that the GGFRC offers a unique opportunity to build well characterized samples for mental health research and to perform genetic studies that so far have not been undertaken in Ethiopia at this scale. We also supported service development, education, and research for strengthening the professional profile of psychiatry and for promoting mental health according to the Action Plans of the World Psychiatric Association (WPA) and to the Sustainable Development Goals (SDG) of the United Nations (UN).

2. THEORETICAL BACKGROUND

Khat trees are native to East Africa and the Arabian Peninsula; their leaves contain amphetamine-like alkaloids and are chewed for their stimulating and euphorigenic effects *(Kalix, 1996)*. Chewing khat has a long tradition among specific ethnic groups but due to increased crop cultivation, it has spread further among the male population. Khat use varies by season: The dry season is characterized by a restricted availability and high market prices, whereas in the rainy season khat is abundantly available and much cheaper. Typical patterns of consumption range from moderate to problematic; excessive use is associated with dependence and khat-induced psychosis *(Odenwald, 2007)*.

Psychotic disorders are serious mental illnesses that often place a high burden on patients, their families, and society in general, especially in low- and middle-income countries *(Rossler et al., 2005; Thornicroft et al., 2004; WHO, 2013)*. People with psychosis and co-morbid substance use disorders often experience deterioration and chronicity of psychosis and public stigma and develop additional somatic and mental health problems *(Foti et al., 2010; Reta et al., 2016; Schmidt et al., 2011; Shibre et al., 2001)*.

Subclinical psychotic symptoms are closer to the healthy state however, and severe psychotic disorders such as schizophrenia are at the other end of a continuum *(van Os et al., 1999)*. Psychotic disorders are rare in the general population (e.g. lifetime prevalence of 0.7% in a large representative sample *(Kendler et al., 1996))*, but subclinical psychotic symptoms are frequent (lifetime prevalence 28% *(Kendler et al., 1996))*; an authoritative review revealed that subclinical psychotic symptoms are transient in 75% to 90% of cases *(van Os et al., 2009)*. Several studies support the continuum model, i.e. individuals with subclinical psychotic symptoms have a higher risk to experience significant persisting problems in social functioning and develop psychotic disorders later in life *(Chapman et al., 1994; Fusar-Poli et al., 2012; Hanssen et al., 2005; Rossler et al., 2007)*.

Environmental factors such as prenatal stress, malnutrition, infection, trauma, growing up in an urban environment and being part of an ethnic minority group are considered to be important in the etiopathogenesis of psychosis. Environmental risk factors associated with stress or dopamine

agonists might also play an important role *(Collip et al., 2008; Murray et al., 2013; van Os et al., 2010).* An environmental risk factor unique to the countries around the Horn of Africa is the chewing of khat leaves, and khat is considered to be Ethiopia's most common substance of abuse *(Odenwald et al., 2017).* Many studies found that excessive khat use can cause dependence and khat-induced psychotic symptoms or disorders *(Odenwald, 2007; Odenwald et al., 2012; Odenwald et al., 2005).* Khat leaves contain amphetamine-like alkaloids, e.g. cathinone, cathine, and norephedrine, which have stimulating and euphorigenic effects on the central nervous system *(Szendrei, 1980)*; cathinone (S (-) alpha-aminopropiophenone) is the main psychoactive component *(Kalix, 1996; Toennes et al., 2003).* Similar to amphetamine, cathinone acts at dopamine receptors in the caudate nucleus and nucleus accumbens to increase dopamine release *(Kalix, 1996; Wabe, 2011).* Amphetamine-induced psychosis remains a matter of ongoing debate *(Phillips et al., 2001; Poole et al., 1996)*: It is unclear whether amphetamine-like substances can cause psychotic disorders in healthy individuals or whether they trigger onset only in individuals with pre-existing, high vulnerability to the disease *(Degenhardt et al., 2018; Phillips et al., 2001).*

Several studies have provided first evidence that the relationship between khat use and psychotic symptoms is moderated by posttraumatic stress disorder (PTSD) and trauma load (i.e. the number of previously experienced traumatic events) *(Odenwald et al., 2009; Widmann et al., 2014). Odenwald et al., (2009)* reported in a sample of 8,124 Somalis that the percentage of respondents with psychotic symptoms increased with the amount of khat use, and this association was much stronger among respondents with PTSD than in those without PTSD.

Different theoretical models exist to explain the positive association of psychopathology and substance use, e.g. the self-medication hypothesis *(Khantzian, 1985)*, trauma hypothesis *(Waldrop et al., 2007)*, and sensitization model of psychosis *(Collip et al., 2008).* The self-medication hypothesis proposes that drugs are used to suppress, control, inhibit or reduce negative affective states *(Boys et al., 2003). Khantzian, (1985)* observed that psychiatric patients often consume substances to cope with sleep disturbances, depression, or intrusive memories. Many other studies found that especially stimulants can affect symptoms of avoidance, numbing, and comorbid depression *(Jacobsen et al., 2001).* The trauma hypothesis assumes that individuals with traumatic experiences are at higher risk to develop psychotic symptoms. Early trauma in particular has been repeatedly linked to various developmental stages of psychotic disorders *(Brady et al., 1998; Coffey et al., 2006; Daly, 2000).* Finally, the sensitization model suggests that repeated

administration of amphetamines and exposure to stress can sensitize dopamine neurons and that the subsequent higher release of dopamine can lead to psychotic symptoms *(Aiello et al., 2012; Redman et al., 2017)*. Repeated or early-life exposure to khat might increase an individual's vulnerability for psychosis *(Yui et al., 2002)*, assuming that psychosis is the result of genetic and acquired vulnerability combined with other environmental triggers, such as traumatic experiences *(Alemany et al., 2011; Howes et al., 2009; Robinson et al., 2015)*. In individuals with a vulnerability for psychosis, khat use may trigger its onset later in life or influence the course of a psychotic disorder *(Odenwald et al., 2005)*.

The present studies aimed to examine in representative samples the effects of the environmental factors *khat use*, assessed objectively, and *exposure to traumatic experiences* on the development of sub-clinical psychotic experiences, a potential vulnerability marker for psychotic disorders. We hypothesized that (1) a biological measure of khat use is associated with the presentation of sub-clinical khat-induced psychotic experiences, (2) the prevalence of khat-induced psychotic experiences is associated with the seasonal availability of khat, and (3) the association between khat use and khat-induced psychotic experiences is particularly prominent in individuals with a high trauma load. In addition, we evaluated (4) whether our findings provided further evidence for the sensitization model of psychosis. Furthermore, we demonstrated (5) the reliability and validity of research methods that are necessary for future genetic studies, i.e. the validity and reliability of pharmacological screening tests as well as assessments performed by trained local interviewers. In addition, (6) we performed genome-wide genotyping in a smaller subset of our sample (N=100) to demonstrate the feasibility of studying genetic risk factors and gene-environment interactions for sensitization models of psychosis, including trauma load and substance abuse. Finally, (7) we examined various aspects of khat consumption such as withdrawal symptoms and also included in our studies specific population groups such as prisoners, in which we examined the relationship between substance use disorders and trauma. Our studies were the first psychopharmacological studies in cooperation between the Institute of Psychiatric Phenomics and Genomics (IPPG) in Munich, Germany, the University of Konstanz in Germany, and the Jimma University (JU) in Ethiopia. Under challenging conditions (high temperatures, limited refrigeration options, lack of infrastructure), we collected biological samples and analyzed them on site. For the High Performance Liquid Chromatography (HPLC) analyses of khat alkaloids in urine samples and for the DNA extraction in blood samples we established new SOPs and laboratory methods at JU.

3. METHODS

3.1 STUDY FIELDS AND GENERAL CONDITIONS

Our studies were conducted at *Jimma University Specialized Hospital (JUSH), in the Correctional Institution in Jimma,* and at the *Gilgel Gibe Field Research Center (GGFRC)* in southwestern Ethiopia.

(1) *Jimma University (JU)* is a center of academic excellence integrating training, research and service development in Jimma town. It is located in the southwest of Ethiopia, about 400 km from the capital Addis Ababa. The University trains professionals at undergraduate and post-graduate levels based on the philosophy of Community Based Education (CBE). *Jimma University Specialized Hospital (JUSH)* recently opened the largest psychiatric facility outside the capital Addis Ababa. The facility has outpatient services and 30 beds for inpatient care. The department is staffed by a full-time psychiatrist and six metal health graduates.

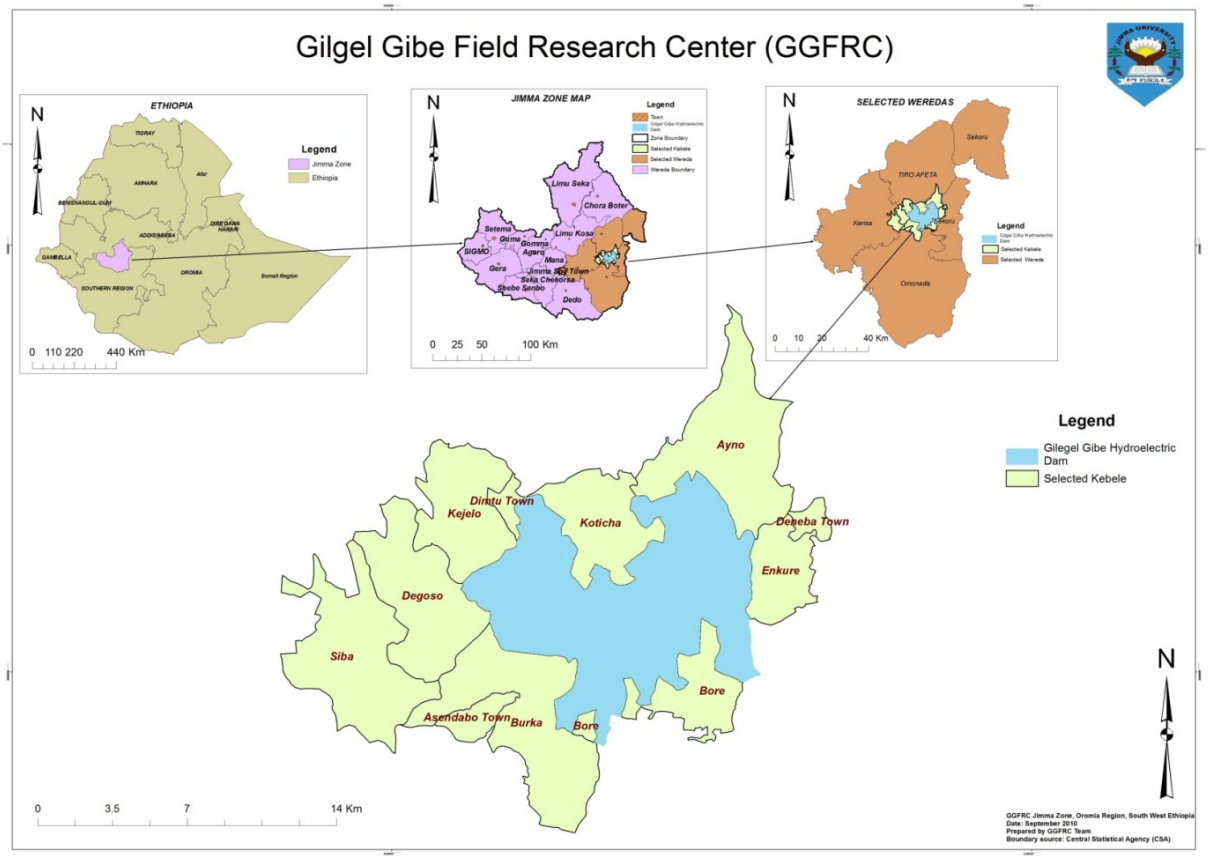
Previous collaborations: In 2009, JU launched a Master of Science (MSc) in Integrated Clinical and Community Mental Health in collaboration with Center for International Health (CIH) at the Ludwig-Maximilians-University (LMU), Munich, Germany. The Ethiopian Ministry of Health and other stakeholders were participating in the consultative meeting for this program. The program aimed at educating non-physician mental health specialists who can perform various clinical, academic, administrative, and research activities in the field of mental health. The two-year program starting in 2010, accepted 5 to 12 students every year. After 9 years, 51 graduated from the program successfully. Meanwhile the master´s graduates make an important contribution to the mental health care in Ethiopia; they work in different and most of all in remote regions of Ethiopia *(Soboka et al., 2018).*

(2) *Correctional Institution in Jimma:* The prison is managed by the Oromiya Regional Correcting Units Administrative Office. It was put into service after the expulsion of the occupying Italian forces in 1943 and serves the following regions: Oromiya, Southern nations and nationalities, and Gambella region. The facility was built to accommodate 450 prisoners but currently houses

about 1460 (1418 male and 42 female). It is designated as a maximum-security facility. The prison population includes offenders on remand and people convicted to a limited or life-long sentence. The prison compound houses a medical clinic and sick bay, in addition to the usual prison facilities.

(3) The *Gilgel Gibe Field Research Center (GGFRC)* is a unique health and demographic surveillance system that belongs to Jimma University. It is located 55 km northeast of Jimma and comprises 8 rural and 3 urban kebeles (the lowest administrative unit in Ethiopia) (s. Figure 1). The population is 30% urban and 70% rural, and more than 60,000 people live in the GGFRC *(Alemseged et al., 2012)*.

Figure 1. Map of Gilgel Gibe Field Research Center (GGFRC)



The primary purpose of the surveillance system is to monitor indicators of basic vital events and generate relevant health, demographic, and socioeconomic information for policies and programs. In addition, the center supports graduate and postgraduate level research undertakings and conducts molecular-to population-level collaborative research with local and international stake-

holders. Different need-based research projects are conducted; the main focuses of research include malaria, causes of death assessed by verbal autopsy, maternal and child health, and chronic non-communicable diseases. The demographics and health of the center's population have been monitored since 2005. Records are updated twice a year. People rarely refuse to comply with programs, because community support for the center is high. In recent years, the construction of a hydroelectric dam in the area has disrupted lives and livelihoods and forced many people to leave their homes and relocate to nearby towns and villages. The majority of residents in both urban and rural kebeles practice subsistence agriculture, producing mainly food crops. In the urban kebeles, water is obtained from a river/stream, shallow dug well, pipes, or protected springs; in the rural kebeles, it is obtained mainly from unprotected sources. The rural kebeles are accessible during the dry season by four-wheel drive vehicles. A recent study on risk factors for non-communicable diseases found that current khat use is highly prevalent among the people living in GGFRC, i.e. 49.9% among males and 13.5% among females *(Alemseged et al., 2012).*

RURAL KEBELE, GGFRC

URBAN KEBELE, GGFRC

3.2 PHENOTYPIC DATA ASSESSMENT

Data collection

The local interviewers were highly trained and experienced staff who had conducted numerous assessments at JU and the GGFRC. Before the studies, they participated in an initial 5-day training conducted by the study teams of local and international experts. The training consisted of a theoretical part on psychiatric experiences and interviewing rules and a practical part that included role plays and supervised interviews. Before expert interviews, the data collectors were retrained for 3 days. Local interviewers have completed at least high school and speak Amharic and Afaan Oromo fluently.

Instruments and measures

Khat and other substance use: Khat chewing was assessed with an adapted version of the Timeline Followback (TLFB) method *(Sobell and Sobell, 1992)*. For the interview day and the previous seven days, respondents indicated the time they had spent chewing khat, their preferred type of khat, and the monetary value of the khat they had consumed. Based on two preparatory studies and in collaboration with local khat experts, we qualitatively defined equivalent standard units of different varieties of khat and their market prices. Respondents who reported no khat use in the previous week were classified as non-users. In most of our studies we as well asked about alcohol use, cigarette/shisha smoking, and use of medications and other substances in the past week.

Psychotic experiences: On the basis of the high prevalence of khat-induced psychotic symptoms in previous population-based studies in khat users, we selected four items of the WHO Composite International Diagnostic Interview (CIDI Core Version 2.1, 12 month version) *(Robins et al., 1988)* to assess the related experiences *(Widmann et al., 2014)*: G2, believing that you are being followed; G2b, thinking that people are talking about or laughing at you; G18, hearing things other people could not hear; and G21, having unusual feelings on your skin or inside your body. Based on of earlier studies, we defined khat-induced psychotic experiences as being present during or up to 6 hours after the last consumption of khat *(Odenwald et al., 2017; Odenwald et al., 2005; Widmann et al., 2014)* and assessed these experiences in the last six months. Because of the transient nature of substance-induced psychotic symptoms, we rated experiences as positive

whether or not the respondent had insight into their psychotic nature and whether or not clinical CIDI criteria were fulfilled (e.g. the interviewer's rating that respondent explanations are implausible).

Traumatic experiences: We used the Life Events Checklist for DSM-5 (LEC-5) *(Weathers et al., 2013)* to screen for potentially traumatic experiences and assessed only the events that were personally experienced or directly witnessed by the respondents. For each item, participants responded (yes/no) to the statement "Happened to me personally, or I witnessed it happen to someone else."

General health: Using the approach described by *Neuner et al., (2008)*, we asked respondents about minor physical complaints in the last four weeks (cough, diarrhea, influenza, fever, headache, stomach ache, other pain, constipation; yes/no). We also asked about problems in functioning related to mental health problems ("Because of your mental health problems, have you been unable to work or fulfill your household or childcare duties during the last four weeks?") and help-seeking for mental health problems ("Have you ever sought help because of mental health problems, e.g. from a traditional healer, religious authority, pharmacy or medical doctor?).

Further instruments: In many studies we have additionally used the following instruments: We assessed the presence of alcohol use disorder (AUD) with the Alcohol Use Disorders Identification Test (AUDIT) *(Babor et al., 2001)* and of nicotine dependence by the Fagerstrom Test for Nicotine Dependence (FTND) *(Heatherton et al., 1991)*. To evaluate khat abuse we also used the Drug Abuse Screening Test (DAST) *(Wazema et al., 2017)*. In addition, cannabis use disorder (Cannabis Use Problems Identification Test, CUPIT) *(Bashford et al., 2010)*, psychopathy (Psychopathy Checklist) *(Hart et al., 1995)*, and social support (Oslo 3-item Social Support Scale) *(Bøen et al., 2012)* were assessed.

3.3 BIOLOGICAL MEASURES

Few studies have addressed methodological issues related to the assessment of khat use, and very little research has attempted to validate research methods that are suitable for field conditions, especially in rural areas which are highly populated by khat users, where electrical power is unavailable and pharmacological laboratory infrastructure not accessible. Khat research is hampered by a lack of validated research methods that can feasibly be used in field conditions, i.e. in areas where most khat users live, far away from sophisticated laboratory infrastructure. Therefore, our aim was to develop khat assessment methods with low resource requirements in order to monitor khat use comprehensively and effectively.

Urine sampling: Urine samples were collected in a clean, wide-mouth standard urine container with a screw cup. During sample collection, containers were codified with robust adhesive labels. Immunoassay tests were performed at the local health centers by trained pharmacological assistants or nurses. Urine samples collected for HPLC were stored in the refrigerators at the local health centers until transported to the laboratory at JU. During transportation to JU, urine samples were stored in battery-powered cold boxes. The mean time from sample collection in the GGFRC until arrival at JU was 299.24 min (minimum 95 min, maximum 495 min). Refrigeration was uninterrupted during transportation and storage at JU. In the laboratory at JU, urine samples were stored according to standard procedures under controlled temperature conditions and appropriate refrigeration (2-8˚C) until the analysis was conducted.

Urine-based immunoassay test: Khat alkaloids in the respondents' urine were assessed by a simple amphetamine immunoassay test (Nal van Minden, Moers, Germany, AMPH mono test, sensitivity 300 ng/ml). In a pre-study in khat users, the test showed good sensitivity and specificity. The test is simple and can be used under field conditions (i.e. at local health centers).
Odenwald et al., (2009) conducted two studies in Somalia to validate commercially available immunoassay tests for detecting and measuring khat alkaloids in urine samples. The tests were standard urine tests for measuring amphetamines: the Combur-10 test (Roche, Switzerland), Oekonomed single amphetamine test (Rödinghausen, Germany), and Diagnostik Nord Multi 5-1 drug test (Schwerin, Germany) *(Odenwald et al., 2009; Odenwald et al., 2005).* All three tests positively detected amphetamines and produced negative results for all other types of drugs. The authors found that both cathine and cathinone can be measured by commercially available tests for amphetamines and that these urine tests are useful and feasible under field conditions in So-

malia *(Odenwald et al., 2009).* In addition, various other research groups have recently used different immunoassays to successfully detect cathinones and synthetic cathinones *(Toennes and Kauert, 2002; Ellefsen et al., 2014; Namera et al., 2015; Swortwood et al., 2014)*. However, the sensitivity of these tests was found to be weak and only excessive khat use appeared to produce a positive test result. Primary analyses revealed that this was also the case for the AMPH 1000 test, and therefore only the results of the AMPH 300 will be reported.

HPLC-based assessment of khat alkaloids: To detect khat alkaloids in urine samples, we used the HPLC method, which was positively evaluated in previous studies *(Yi et al., 2013; Atlabachew et al., 2016; Atlabachew et al., 2017; Morad et al., 1989; Toennes and Kauert, 2002; Toennes et al., 2004))*. Toennes and Kauert were among the first researchers to use the HPLC method to analyze urine samples of khat users *(Toennes and Kauert, 2002)*. Khat alkaloids were detected in urine samples up to 34 hours after khat chewing, and in one case even up to 50 hours afterwards *(Toennes and Kauert, 2002)*. Not studied at all were biases that are typical for the assessment of self-reported data, e.g. social desirability, which might cause underreporting of substance use. Our first aim was to determine the degree of concordance between assessment methods with low-resource requirements that are feasible for field research, i.e. interviews with trained laypersons and simple immunoassay tests originally developed to measure amphetamines, and large-scale application and gold standard assessment methods with high resource requirements and thereby to assess the validity of the low-resource methods. Our second aim was to deepen our understanding of self-reported khat use, i.e. how specific aspects relate to the biological measures. Therefore, we analyzed norephedrine (NE) as the sole marker for khat alkaloids because it is one of the main, stable alkaloids that can still be detected more than one day after khat use, and it is a legal substance in Ethiopia.

Reference preparation: Twenty Recatol® capsules were weighed, the contents removed and the average weight of each capsule calculated. About 50 mg NE-equivalent weight of Recatol® was mixed with 10 ml of water, and the pH was adjusted to 9 by adding NaOH. NE was extracted via 10 ml of dichloromethane:diethylether (mix 1:1); this step was conducted twice. The organic ingredients were removed with a separatory funnel, and the aqueous part containing NE was evaporated to dryness. Finally, the dry residue was dissolved in 100-500 µl methanol and analyzed by HPLC.

Urine sample preparation by solid phase extraction (SPE): SPE was performed with Agilent Vac Elut 12 Manifold and Bond Elut LRC-Certify, 300 mg. Urine samples were conditioned at room

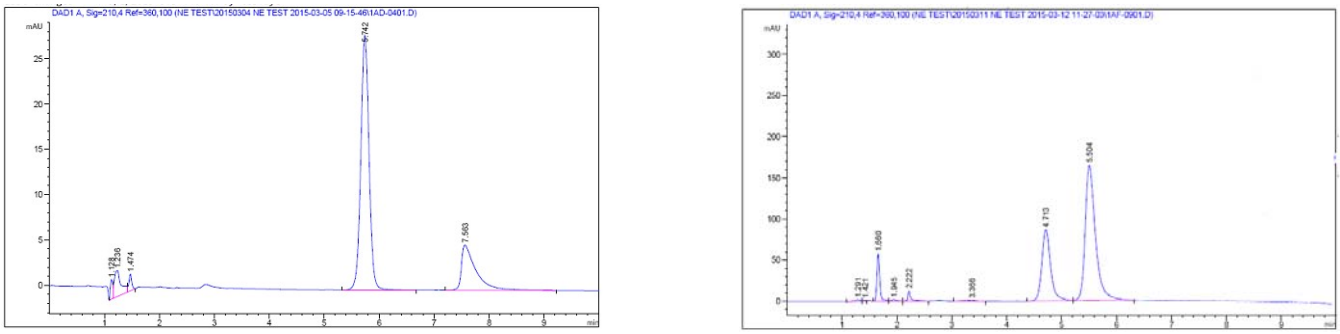
temperature. Then, 1.0 ml of the urine sample was diluted with 4.0 ml of phosphate buffer. The SPE column was conditioned with 3.0 ml methanol and 3.0 ml phosphate buffer. The diluted sample was applied on the SPE column and extracted with a vacuum sucker at a pressure of 5 inHg. The sample was washed from the column by the application of 2.0 ml of 0.1M acetic acid and 3.0 ml of methanol. Then, the sample was eluted from the column into a new test tube by 3.0 ml of dichloromethane : isopropanol : ammonia (80:20:2, v/v) and evaporated to dryness. Finally, the sample was dissolved into 2.0 ml of diluents solvent and analyzed by HPLC.

Preparation of reagents: Mobile phase buffer solution was freshly prepared by dissolving 13.6 g potassium phosphate monobasic (KH2PO4) in 1000.0 ml water. Mobile phase was then freshly prepared by mixing 30.0 ml methanol with 970 ml mobile phase buffer solution. The solution was then filtered through a 0.45 µm nylon filter and degassed under vacuum. For conditioning, 3.0 ml methanol and 3.0 ml phosphate buffer (0.1M, pH 6) was used. For the SPE washing solution, 2.0 ml acetic acid (i.e. 5.73 ml glacial acetic was added to water adjusted to 1 L to obtain 0.1 M) and 3.0 ml methanol were used. As the SPE elution solvent, 3.0 ml dichloromethane : isopropanol : ammonia (25%; 80:20:2, v/v) was used. Diluents were prepared by mixing 30.0 ml methanol with 970.0 ml water. Then, 1.3 g KH2PO4 was added and stirred until all the salt was dissolved, then the whole solution was degassed.

HPLC-results: The typical chromatograms obtained on Recatol® reference standard solution and the urine extracts is presented in Figure 2. NE elutes at an average retention time of 5.7 min with peak asymmetry As of 1.1 and retention factor k' of 4.2. The number of theoretical plate N was calculated to be 1156 indicating good separation efficiency of the column. Method validation results indicated the fitness-for-use of the applied HPLC method. The 95% CI for the regression slope = 5.925 (95% CI: 5.796 to 6.053) and y-intercept = 3.476 (95% CI: -25.960 to 32.913) together with r2 value of 0.999 and ANOVA F-value of 21548 proved a strong positive linear relationship. Percentage relative standard deviation for repeatability (%RSD= 0.10) of the method were within the specification limit (%RSD ≤2). Limit of detection (LOD) for this method was 0.04 µg/ml and limit of quantification of 0.14 µg/ml show that the method fits for both qualitative and quantification analysis. Before analysis, the samples were inspected for integrity and found to be stable to the storage condition.

Figure 2. HPLC-results: Norephedrine (NE) elutes at an average retention time of 5.7 min with peak asymmetry.

A) RECATOL (reference standard) B) URINE SAMPLE



Urine samples: A total of 126 urine samples were extracted using the solid-phase extraction (SPE) apparatus and analysed by HPLC. The results showed that 81 (64.3%) samples were positive and the remaining 45 (35.7%) samples were negative for NE. For positive urine samples, the NE content ranges from 2.3 to 161.1 µg/ml, with an average NE content of 36.7 µg/ml.

3.4 GENETIC ANALYSES

We performed genome-wide genotyping in a smaller subset of our pilot sample (N=100). This pilot study was conducted to demonstrate the feasibility of studying genetic risk factors and gene-environment interactions for sensitization models of psychosis, including trauma load and substance abuse, in the full Ethiopian cohort of 10,000 individuals. We collected blood samples (10 ml venous blood). The samples were transported to the study laboratory by a cold chain system preserving the integrity of the sample and stored in refrigerators at 2-8 °C after reaching the laboratory. Subsequently, blood samples were transported to JU and stored in freezers (-80℃). The average time from sample collection at the GGFRC until arrival at JU was 299,24 min (range 95-495 min). For DNA extraction, we established state-of-the-art procedures on site: DNA was extracted using chemagic DNA Blood 10k Kits (Perkin Elmer). The purity and homogeneity of the samples were tested by spectrophotometric measurements. For photometric determination of the DNA concentration, we used BioPhotometer instruments with absorbance measured at 260 nm. The samples were genome-wide genotyped using the Infinium Global Screening Array BeadChip (Illumina). This BeadChip includes multi-ethnic genome-wide content which was selected at minor allele frequencies of >1% across all 26 1000 Genomes Project populations, including cohorts from Africa *(Huang et al., 2011; Ha et al., 2014; Auton et al., 2015).* We also performed downstream analyses of our GWAS pipeline to further assess the quality and usability of our data. This included a principle component analysis (PCA) using the EIGENSOFT software package (with default parameters) as well as an example GWAS on NE concentration in urine for our study sample *(Li Q et al., 2008)*.

4. PRESENTATION OF THE HABILITATION-RELEVANT ORIGINAL WORKS

4.1 **Adorjan K**, Odenwald, M., Widmann M, Tesfaye M, Tessema F, Toennes S, Suleman S, Papiol S, Soboka M, Mekonnen Z, Rietschel M, Pogarell O, Susser E and Schulze TG. Khat (catha edulis) use and the occurrence of psychotic symptoms in the general population in Southwestern Ethiopia: suggestive evidence for sensitization by traumatic experiences. *World Psychiatry.* 2017 16(3):323.

Introduction

The sensitization model of psychosis suggests that repeated exposure to amphetamines or stress can sensitize dopamine neurons. Khat leaves contain amphetamine-like alkaloids, and heavy use is frequently associated with psychotic symptoms. We studied how seasonal variations in khat availability and exposure to traumatic events affect khat-induced psychotic experiences. At GGFRC of JU, we randomly selected a representative cohort of 1,100 men aged 18 to 40 years; 853 (77.5%) agreed to participate. We interviewed participants during the dry season, when khat availability is restricted, and nine months later, just after the rainy season (n = 695; 81.5% of initial sample). We assessed self-reported khat use, khat-induced psychotic experiences, and exposure to potentially traumatic experiences. Khat alkaloids were determined in urine by immunoassay. Khat use and khat-induced psychotic experiences were more prevalent during the rainy season and in participants with a positive immunoassay and higher trauma load. During the rainy season, khat use and trauma interacted and increased the prevalence of khat-induced psychotic experiences. Recent and lifetime trauma were equally associated with more khat-induced psychotic experiences. Our findings support that environmental factors and sensitization might be related to the development of psychotic experiences but need to be replicated in larger, longer studies that assess psychotic experiences and symptoms more comprehensively.

Methods

Study population: This study was conducted at the GGFRC. We used a two-stage process to randomly select 1,100 male adults (18-40 years) from the GGFRC central database. First, we randomly chose two urban and three rural clusters. Then, we randomly selected participants on the basis of the overall proportion of the cluster subpopulation size. Inclusion criteria were male sex, age 18-40 years, residency in the GGFRC for at least 6 months, and fluency in Amharic or Afaan Oromo. We recruited only men because in the GGFRC significantly more men than women use khat *(Alemseged et al., 2012)*. We chose the age range because khat use typically starts in young adulthood, khat is used mostly by young males, and psychotic experiences usually appear for the first time at a young age *(Kebede et al., 2005; McGrath et al., 2016; Reda et al., 2012).* Exclusion criteria were plans to relocate within the study period, severe alcohol or other substance abuse, and severe developmental and neurological disorders.

Study design: Trained local interviewers assessed the participants twice at nine-month intervals (T1 and T2) to determine khat use and traumatic experiences and the presence and stability of distinct khat-induced psychotic experiences. At T1 and T2, urine samples were collected and assessed for khat alkaloids by immunoassay. T1 was in the dry season (February and March 2015), when khat supply was limited and khat was expensive, and T2 was shortly after the rainy season (November and December 2015), when khat was abundantly available at local markets and prices were low.

Validation sub-study: The validity of the data was confirmed by clinical validation interview conducted shortly after T1 (mean [SD] 2.0 [1.9] days after T1) by mental health specialists, who reassessed psychotic experiences and khat and alcohol use in a randomly selected subgroup of 124 individuals. In this subgroup, we obtained an additional urine sample, which was refrigerated until being transported to JU laboratory for analysis by HPLC to validate the immunoassay results *(European Directorate for the Quality of Medicines, 2006; Roman, 2004; Toennes and Kauert, 2002)*. We chose the khat alkaloid NE as the single reference substance for practical reasons (it is detectable for longer periods, and the pure substance is not illegal in Ethiopia). To control for NE consumption in common cold medications, we assessed the use of these medications and subsequently excluded 4 participants from the validation study. The immunoassay and HPLC (reference) showed a moderate agreement (unweighted kappa .419). Specificity was perfect (1.00), but sensitivity was only moderate (.506) because, in contrast to HPLC, immunoassay cannot detect

small amounts of khat alkaloids; in line with this, the urine level of NE in respondents with a negative immunoassay who reported khat chewing was significantly smaller than in respondents with a positive immunoassay ($p < .001$). Consequently, we considered the immunoassay test rather a screening measure for heavy khat use only. Immunoassay also showed moderate agreement with self-reported khat use (because of the typical metabolism of khat alkaloids, we used self-reported khat use for the day of the sampling plus the day before as reference), with an unweighted kappa of .453, a specificity of .675, and a sensitivity of .827. In sum, the results of the validation sub-study support the validity of the immunoassay tests used.

Instruments and measures (s. above - here only supplemented with some study-specific information)

Khat and other substance use: Khat chewing was assessed with an adapted version of the Timeline Followback (TLFB) method *(Sobell and Sobell, 1992)*. A comparison of khat use assessed by the trained local interviewers and by trained mental health experts confirmed the validity of the assessment (kappa = .798; $p <.001$); in the expert interview, 76.0% of participants (n = 111) reported khat use in the previous week.

Psychotic experiences: On the basis of the high prevalence of khat-induced psychotic symptoms in previous population-based studies in khat users, we selected four items of the WHO Composite International Diagnostic Interview (CIDI Core Version 2.1, 12 month version) *(Robins et al., 1988)* to assess the related experiences *(Widmann et al., 2014) (s. above).* We calculated a dichotomous variable from the responses to the four items, i.e. whether or not any khat-induced psychotic experience was reported. The agreement between local interviewers and mental health experts was moderate (kappa = .553); specificity was high (.934) and sensitivity, moderate (.576). In sum, the validity of the local interviewer ratings was acceptable for our analysis because the majority of cases and non-cases were correctly classified. In the validation sub-study, the agreement of khat-induced psychotic experiences with true psychotic symptoms (assessed by mental health experts) was small (Phi = .276, p = .002): 65% (n = 80) had no psychotic symptom or experience, 10% (n = 12) had both types of psychotic phenomena, 17% (n = 21) had only khat-induced psychotic experiences, and 9% (n = 11) had only true psychotic symptoms, i.e. more than half of those with true psychotic symptoms also had khat-induced psychotic experiences.

Traumatic experiences. We used the Life Events Checklist for DSM-5 (LEC-5) *(Weathers et al., 2013)* to screen for potentially traumatic experiences and assessed only the events that were personally experienced or directly witnessed by the respondents. At T1, we used the LEC-5 to assess previous traumatic experiences (exposure before T1); and at T2, to assess events in the nine months since T1 (recent exposure). Lifetime exposure was defined as the sum of events reported at T1 and T2. We used a median split to build two groups (low vs. high lifetime exposure): ≥4 lifetime traumatic events corresponded with a high trauma load, and ≤3, with a low trauma load. Exposure before T1 was defined as ≥3 previous traumatic events. All respondents who reported at least one recent event at T2 were included in the group with recent exposure.

General health: Using the approach described by *Neuner et al., (2008)*, we asked respondents about minor physical complaints in the last four weeks *(s. above)*. We recorded a "1" for each complaint that achieved an acceptable Cronbach's alpha of .656 and then calculated a sum score to represent participants' general physical health.

Immunoassay tests: Khat alkaloids were assessed in urine by simple immunoassay tests (Nal van Minden immunoassay test, Nal van Minden, Moers, Germany; amphetamine mono test, cut-off 300 ng/ml) at T1 and T2. Urine samples were collected in a clean wide-mouth standard urine container with a screw cup and transported within hours to a local health center, where they were refrigerated.

Statistical analysis: We tested for group differences with paired t-tests and McNemar's test and evaluated whether khat use differed in the four subgroups (trauma load * test result) with a two-factorial analysis of variance (ANOVA). We evaluated the effect of khat alkaloids and trauma load on psychotic experiences with Chi2 tests; the null hypothesis was that the cell frequencies in the 2*2 (trauma load * test result) and 2*2*2 tables (trauma load high vs. low * immunoassay test positive vs. negative * khat-induced psychotic experiences present vs. absent) were equally distributed. We repeated this analysis in a 2*2*2*2 table by splitting the trauma factor into exposure before T1 and recent exposure (between T1 and T2). For the graphical presentation, we calculated the standard error of sample proportions by binomial distribution. Furthermore, we used binary logistic regression to test whether khat-induced psychotic experiences can be statistically explained by the immunoassay test for khat alkaloids (positive vs. negative) or trauma load (median split; high vs. low trauma load), or their interaction. These three terms were entered simultaneously into the model, together with a constant term. We did not control for socio-demographic

variables and studied main and interaction effects. To increase power, we restricted this binary logistic regression model to respondents who reported khat use in the previous week.

Results

Comparison at T1 and T2: At T2, 695 (81.5%) of the 853 respondents at T1 were reassessed. Table 1 shows the sample characteristics at T1 and T2. The mean age at T2 did not differ significantly from T1; however, the 158 respondents who could not be reinterviewed at T2 were slightly younger than the rest of the sample (mean [SD] age 27.5 [6.5] years; p = .045; Hedge's g = .178). The proportion of participants reporting mental health-related problems in functioning and having ever sought mental health assistance decreased significantly from T1 to T2; however, rates of help-seeking (p = .794) and problems in functioning (p = .291) were similar in participants who did not participate at T2 and those who did. Reported physical complaints decreased significantly from T1 to T2. Participants who dropped out reported a similar number of physical complaints (p = .737) and of potentially traumatic experiences at T1 (p = .438).

Table 1: Sample characteristics of male khat users at the initial assessment (T1, dry season) and 9-month follow-up assessment (T2, rainy season). For age, traumatic experiences, and the sum of physical complaints, we report an independent t-test between the participants included at T2 and those who had dropped out; for all other variables, we performed a paired McNemar's test. *n values vary because of missing data.

	T1 (N = 853)	**T2 (N = 695)**	**p**
Mean (SD) age in y	28.4 (6.6), (n = 850)	28.6 (6.6), (n = 693)	.045
Self-reported khat use in the past week, % (n/N*)	72.1 (606/841)	80.1 (555/693)	<.001
Positive immunoassay test, % (n/N*)	28.3 (239/813)	36.9 (246/666)	<.001
Alcohol use in the past week, % (n/N*)	6.9 (58/842)	6.2 (53/694)	.121
Cigarette or shisha use in the past week, % (n/N*)	13.3 (105/791)	16.0 (110/688)	.141
Medication and other substance use in the past week, % (n/N*)	10.3 (86/831)	17.9 (124/691)	<.001
Problems in functioning in the past 4 weeks due to mental health problems, % (n/N*)	4.1 (35/842)	1.4 (12/693)	.001
Ever sought help because of mental health problems, % (n/N*)	2.3 (19/841)	0.7 (5/694)	.003
Khat-induced psychotic experiences in the past 6 months, % (n/N*)	7.9 (67/853)	12.8 (89/693)	.001
Physical complaints in the past 4 weeks, mean (SD)	2.0 (1.8), n = 843	1.6 (1.6), n = 694	.001
Potentially traumatic experiences, mean (SD)	3.2 (2.5), n = 842	0.5 (0.9), n = 694	.438

Prevalence of khat use, psychotic experiences, and traumatic experiences: At T1, 599 (71.1 %) individuals reported khat use in the previous week, and at T2, 565 (81.4%; p < .001). Immunoassay tests were positive in 28.3% (T1) and 36.9% (T2; p <.001) of all samples (khat users and non-users) and in 37.6% (T1) and 44.2% (T2) of khat users. The 6-month prevalence of khat-induced psychotic experiences was 7.9% at T1 and 12.8% at T2 (p = .001).

The cross-tabulation reported in Table 2 shows the great variability in the prevalence of khat-induced psychotic experiences between the dry and rainy season: 70.8% of the respondents with khat-induced psychotic experiences at T2 had none at T1, and 54.4% of the respondents with these experiences at T1 had none at T2.

Table 2. Cross-tabulation of khat-induced psychotic experiences in a sample of male khat users between the assessments in the rainy season (T2; n = 695) and dry season (T1; n = 853). We report frequencies and percentages of the total sample.

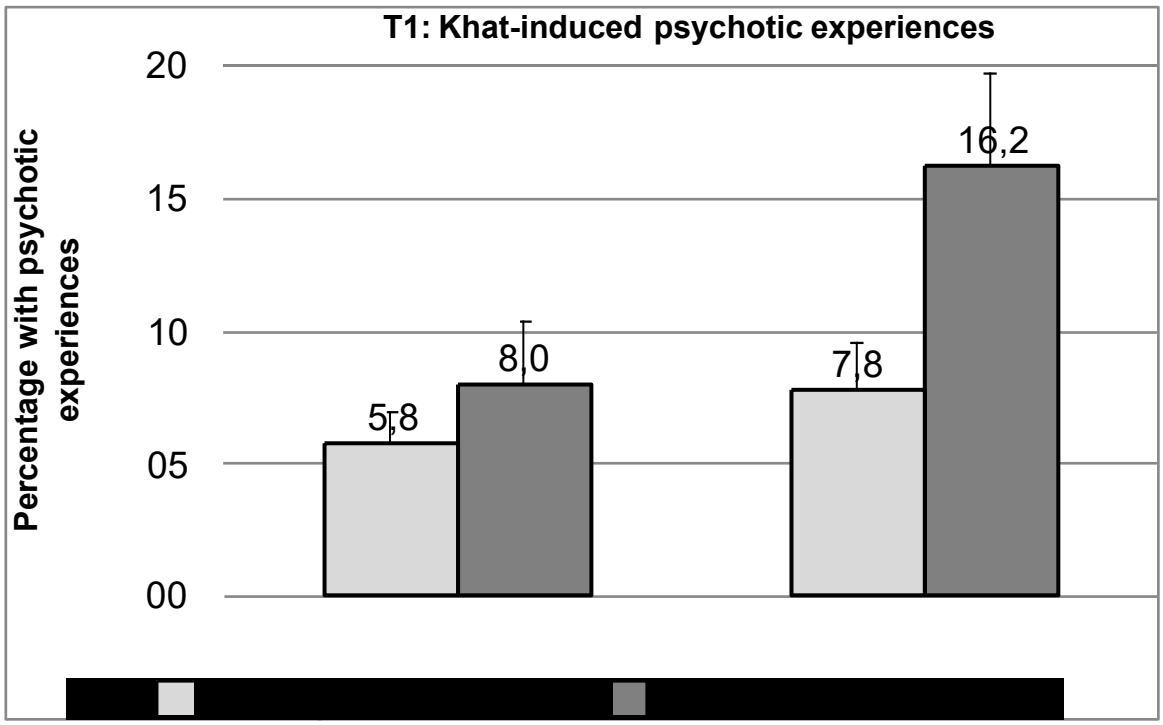
		Khat-induced psychotic experiences at T2		**Sum**
		No %	**Yes n, n, %**	
Khat-induced psychotic experiences at T1	**No**	573, 82.7%	63, 9.1%	636, 91.8%
	Yes	31, 4.5%	26, 3.8%	57, 8.2%
Sum		604, 87.2%	89, 12.8%	693, 100%

A total of 743 (87.1%) respondents reported at least 1 event on the LEC-5 before T1, and 206 (29.7%) reported at least 1 event during the 9 months between T1 and T2. A mean of 3.7 (SD 2.7) events were reported. The most common potentially traumatic experiences were fire or explosion (64.5%), physical assault (51.0%), unexpected death of close people (33.9%), life-threatening illness/injury (30.8%), transportation accident (25.8%), severe human suffering (24.2%), assault with a weapon (21.3%), and natural disaster (19.9%).

Predicting psychotic experiences by khat use and traumatic experiences

Dry season (T1): Of the 853 respondents, 813 could be included in the analysis (95.3%; data were missing for the remaining 40), which was based on a 2 (high vs. low trauma load) * 2 (positive vs. negative immunoassay test) * 2 (with vs. without khat-induced psychotic experiences) table. The percentage of khat-induced psychotic experiences was highest (16.6%) in the group with a positive immunoassay test and high trauma load (s. Figure 3).

Figure 3. Predicting psychotic experiences by khat use and traumatic experiences. Dry season

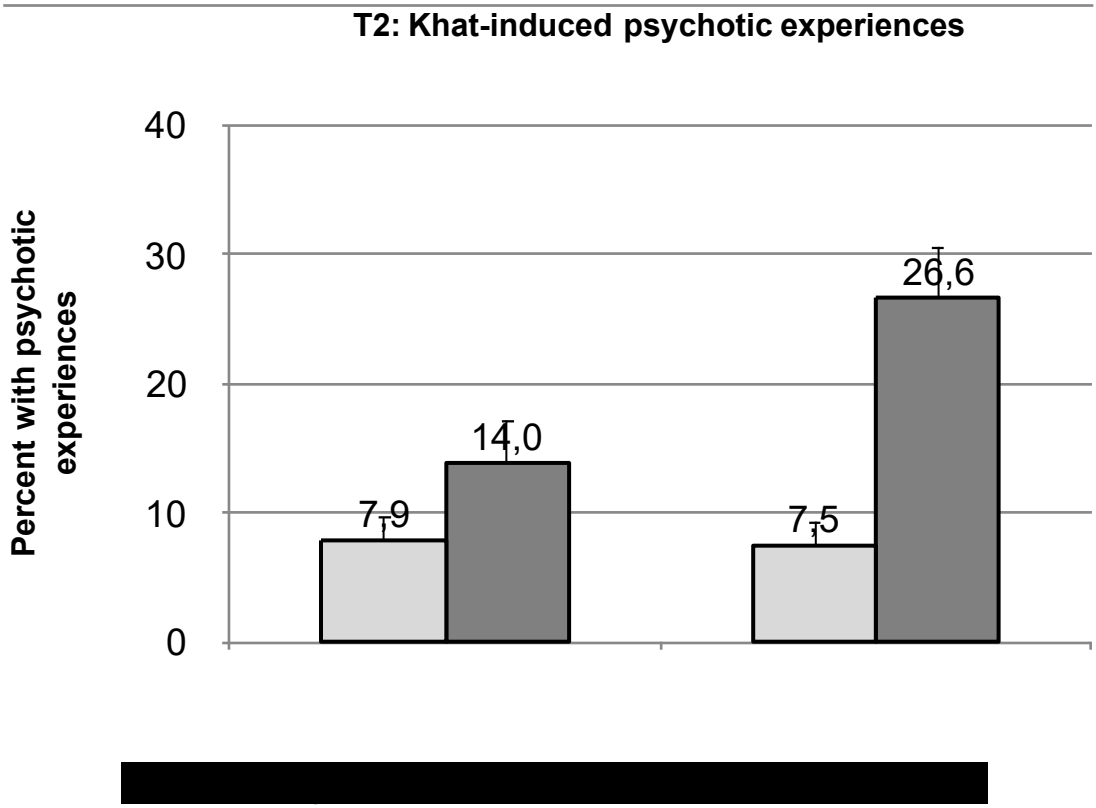


The 2*2 table (low trauma load * positive immunoassay test) with the 489 respondents with a low trauma load did not reach statistical significance (Chi2 = 0.780, df 1, p = .377). In the 324 respondents with a high trauma load, both the 2*2 table (Chi2 = 5.367, df 1, p = .021) and the total 2*2*2 table (Chi2 = 6.112, df 1, p = .013) were significant. The binary logistic regression model with the 813 respondents in which the trauma load and immunoassay test and their interaction were entered into a single block achieved a significant overall fit (Chi2 = 10.281, df 3, p = .016). No significant main effects (trauma load: OR = 1.375, CI 95% .709-2.667, p = .347; immunoassay test: OR = 1.420, CI 95% .650-3.105, p = .379) or a significant interaction effect (OR = 1.616, CI 95% .559-4.671, p = .375) were detected. We repeated the binary logistic regression model in the current khat users (n = 599, 70.2% of the T1 sample): 580 could be included, and

the model did not achieve a significant fit (Chi2 = 6.627, df 3, p = .085). Neither the main effects nor the interaction effect was significant (p > .308).

Rainy season (T2): At T2, 693 respondents were re-assessed, and 661 (95.4%) were included in the analysis. Similar to T1, the percentage of khat-induced psychotic experiences increased with a positive amphetamine urine test and high trauma load (s. Figure 4). Among those with a low trauma load (n = 350), a positive urine test was not related to the proportion of khat-induced psychotic experiences (Chi2 = 3.370, df 1, p = .066), but in those with a high trauma load (n = 311), it was associated with a higher proportion of khat-induced psychotic experiences (Chi2 = 21.261, df 1, p < .001). The overall test for the whole 2* 2*2 table was also significant (overall Chi2 = 22.909, df 1, p < .001).

Figure 4. Predicting psychotic experiences by khat use and traumatic experiences: Rainy season



The binary logistic regression model with all 661 respondents achieved a good model fit (Chi2 = 28.140, df = 3, p < .001). The main factor trauma load did not achieve significance (OR = .949, CI 95% .459-1.962). Both the immunoassay test main effect and the interaction effect showed a trend towards significance (immunoassay: OR = 1.916, OR 95% .948-3.871, p = .070; trauma * immunoassay: OR = 2.339, CI 95% .883-6.197, p = .088). When the binary logistic regression

model was limited to khat users (because of missing data, 540 of 565 khat users were included), we found a good model fit (Chi2 = 18.697, df 3, p < .001). There was no main effect of trauma load (OR = .829, CI 95% .388-1.774, p = .630) or immunoassay test (OR = 1.314, CI 95% . 634-2.724, p = .463), but a significant interaction effect of amphetamine test * trauma load (OR = 2.822, CI 95% 1.030-.732, p = .044). In an additional analysis, we evaluated khat use in the four groups to investigate whether the higher proportion of khat-induced psychotic experiences in some subgroups might simply be related to a higher khat use, i.e. positive or negative immunoassay * high or low trauma load * hours of khat use in the previous week in the dry (T1) and rainy (T2) seasons (s. Table 3). There were no significant differences.

Table 3. Hours of actual khat use in participants who used khat in the week before the assessments T1 (dry season; n = 853) and T2 (rainy season; n = 695) and had a high or low trauma load.

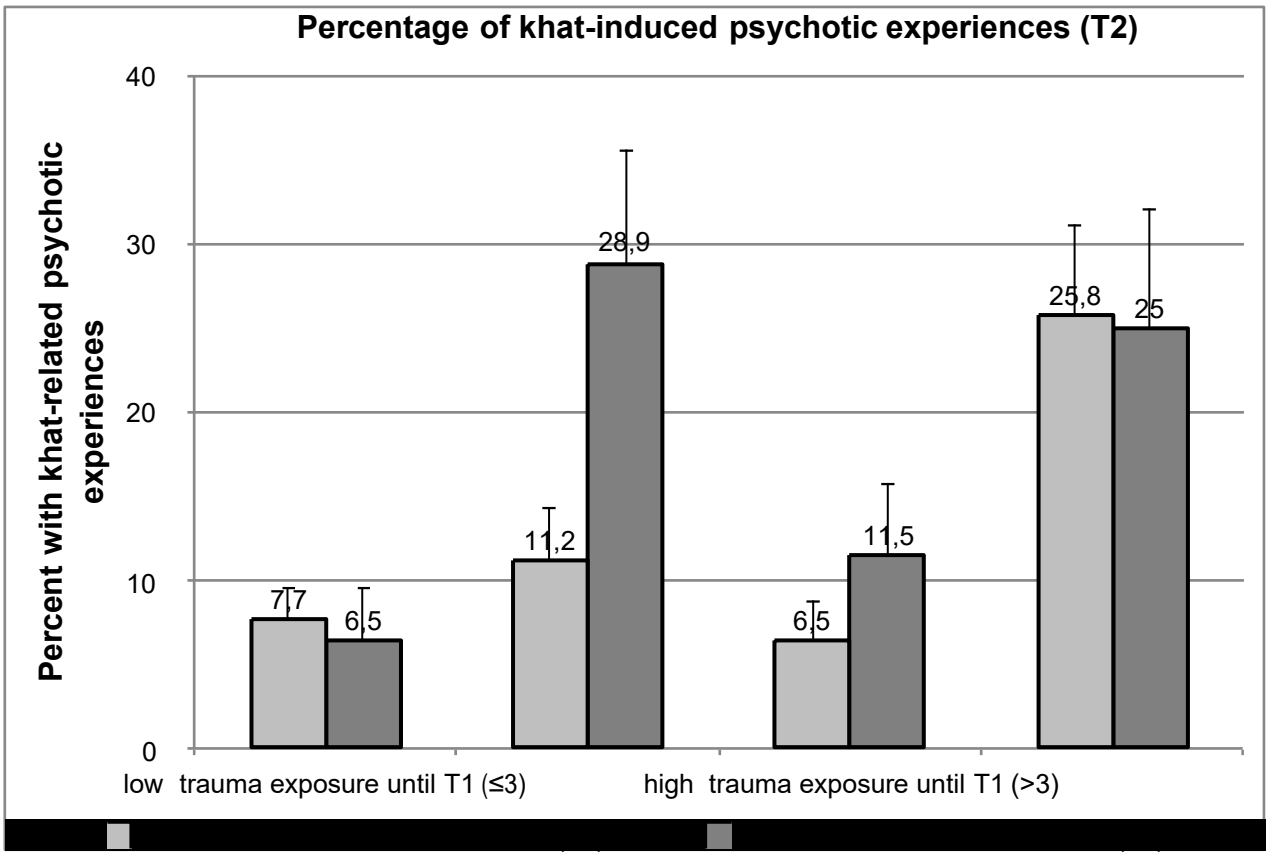
	Low Trauma Load		**High Trauma Load**		**ANOVA**	**Post hoc t-test[2]**
	(1) **Neg Test[1]**	(2) **Pos Test[1]**	(3) **Neg Test[1]**	(4) **Pos Test[1]**		
Mean (SD) hours of khat use (past week) in the dry season (T1)	8.28 (9.88), n = 218	15.12 (14.16), n = 117	8.58 (8.79), n = 144	19.41 (16.86), n = 101	Trauma: p = .028 Immunoassay: p < .001 Interaction: p = .057	(1) vs. (3): p = .765 (2) vs. (4): p = .043
Mean (SD) hours of khat use (past week) in the rainy season (T2)	12.52 (12.21), n = 157	23.68 (21.33), n = 112	16.88 (17.05), n = 141	26.25 (21.70), n = 121	Trauma: p = .029 Immunoassay: p < .001 Interaction: p = .565	(1) vs. (3): p = .013 (2) vs. (4): p = .368

1. Presence of khat alkaloids in urine were tested with the Nal van Minden immunoassay test; Neg: negative; Pos: positive.
2. Bonferroni correction, alpha = .025

Effect of recent and lifetime trauma on khat-induced psychotic experiences: To study the effect of recent vs. lifetime exposure to potentially traumatic events, we analyzed the data of the 660 respondents who reported potentially traumatic experiences at T1 and T2 and compared rates of reported khat-induced psychotic experiences in a 2*2*2*2 table, i.e. (low vs. high trauma load before T1) * (with vs. without recent trauma in 9 months before T2) * (positive vs. negative immunoassay test) * (with vs. without khat-induced psychotic experiences). The rates of reported khat-induced psychotic experiences among the groups with negative immunoassay tests ranged from 6% to 12%; and among the ones with positive test results, from 11% to 29% (s. Figure 5).

In the sub-sample of 399 respondents who reported low trauma exposure before T1, 28.9% of the respondents with recent trauma exposure and a positive immunoassay had khat-induced psychotic experiences. Among the 261 respondents with trauma exposure before T1, the two groups with trauma exposure and a positive immunoassay reported similarly high rates of khat-induced psychotic experiences, irrespective of whether the trauma exposure was recent (25.0%) or not (25.8%).

Figure 5. Effect of recent and lifetime trauma on khat-induced psychotic experiences



Discussion

This study found first potential evidence that the prevalence of khat-induced psychotic experiences might be increased by two environmental factors: higher seasonal khat availability and greater exposure to traumatic experiences. This study is the first to report on this potentially serious problem in Ethiopia. The findings may be relevant in other low-income countries where khat chewing is highly prevalent. Recent exposure to traumatic events seemed to have the same effects on psychotic experiences as lifetime exposure. The rate of khat-induced psychotic experiences was highest among respondents with high exposure to traumatic events and a positive khat alkaloid test; more extreme khat use did not explain the higher rate in this subgroup. As such, our data might support the interpretation that these two environmental factors interacted with each other in participants with recent or lifetime exposure to traumatic events to make them more susceptible to the psychotomimetic effects of khat. This suggested interaction needs further proof, but it is alarming that large parts of a population are exposed to khat alkaloids. Although it is unsurprising that higher khat use could be related to higher rates of khat-induced psychotic experiences, the hypothesis that higher vulnerability to psychotic symptoms might result from the interaction of the two environmental factors is important and warrants further study. The change between the two measurements in khat-induced psychotic experiences in our sample was similar to the changes in subclinical psychotic symptoms in the NEMESIS study *(Hanssen et al., 2005)*, and the finding that experiences were not strongly related to true psychotic symptoms was similar to other studies on the psychotic continuum *(van Os et al., 2009)*.

Khat-induced psychotic experiences can be seen as a marker of individual vulnerability to psychosis in the sense of a gene x environment interaction *(Linney et al., 2003; McDonald et al., 2001)*, as has been shown for other non-clinical forms of psychotic presentations *(Linney et al., 2003)*. Our study is compatible with the view that environmental variation is related to patterns of psychotic experiences and that vulnerability to psychotic disorders arises from a combination of environmental factors. In our sample, the vulnerability marker of khat-induced psychotic experiences seemed to vary systematically with current khat use (assessed by immunoassay) and experience of potentially traumatic events: The prevalence of khat-induced psychotic experiences was highest among respondents with a positive khat test and high trauma load or recent trauma exposure. This association was strongest during the rainy season (T2), when market availability and khat use were higher and more respondents reported psychotic experiences; all these factors might have lowered the threshold to make this environment-induced vulnerability visible in this

specific context. This finding needs to be further examined in longitudinal cohort studies that assess harms to public mental health with clinical outcomes (e.g. psychotic and other mental disorders).

Our interpretation that the reported findings might be explained in the context of the sensitization hypothesis is further strengthened by our more complex analyses. This hypothesis would predict that both, recent and lifetime trauma would have measurable effects. In our study we measured exposure to potentially traumatic events at T1 and divided the group into subgroups with high and low previous trauma exposure. At T2, we assessed traumatic events in the 9 months since T1 (recent exposure) and divided the group into those with any traumatic events in this period and those with at least one such event. Among respondents with a positive immunoassay test and low trauma exposure before T1, only those with recent trauma exposure had a higher prevalence of khat-induced psychotic experiences. The prevalence of khat-induced experiences was high among respondents with a positive immunoassay test and high exposure to traumatic events before T1, and recent traumatic events had no additional effect. Our results are compatible with the hypothesis that the dopamine system becomes sensitized in the long term to the psychotomimetic effects of khat after exposure to traumatic experiences; we showed that experiencing recent traumatic events might be associated with a prevalence of khat-induced psychotic experiences similar to that of earlier exposure and that recent exposure might not be related to an increase in khat-induced psychotic experiences in individuals who already have a high level of exposure.

In this study, we additionally validated measures of khat use that require few resources and training compared with gold standard assessment tools. We showed that low-resource methods to assess khat use under field conditions have a high concordance with methods that require highly trained staff and sophisticated laboratory environments. We conclude that the assessment of khat use by trained local staff and the application of a simple immunoassay test that was originally developed for amphetamine assessment are valid research tools.

4.2 **Adorjan K**, Mekonnen Z, Tessema F, Ayana M, Degenhardt F, Hofmann P, Fricker N, Widmann M, Riedke H, Toennes S, Soboka M, Suleman S, Tesfaye M, Rietschel M, Susser E, Odenwald M, Schulze and Mattheisen M. Genotype-Phenotype feasibility studies on khat abuse, traumatic experiences and psychosis in Ethiopia. *Psychiatr Genet*. 2019; 30(1):34-38.

Introduction

In addition to our first study reported above (s. publication 4.1), we also performed genome-wide genotyping in a smaller subset of our pilot sample (N = 100). This second pilot study was meant to show the feasibility of studying the involvement of genetic risk factors and gene-environment interactions for sensitization models of psychosis including trauma load and substance abuse. Our aim was to investigate the link between mental illness and its environmental and genetic risk factors in low-income countries. Studies like these will improve our understanding of how risk factors identified predominantly in high-income countries also apply to other settings and will identify new, sometimes population-specific risk factors.

Methods (s. above)

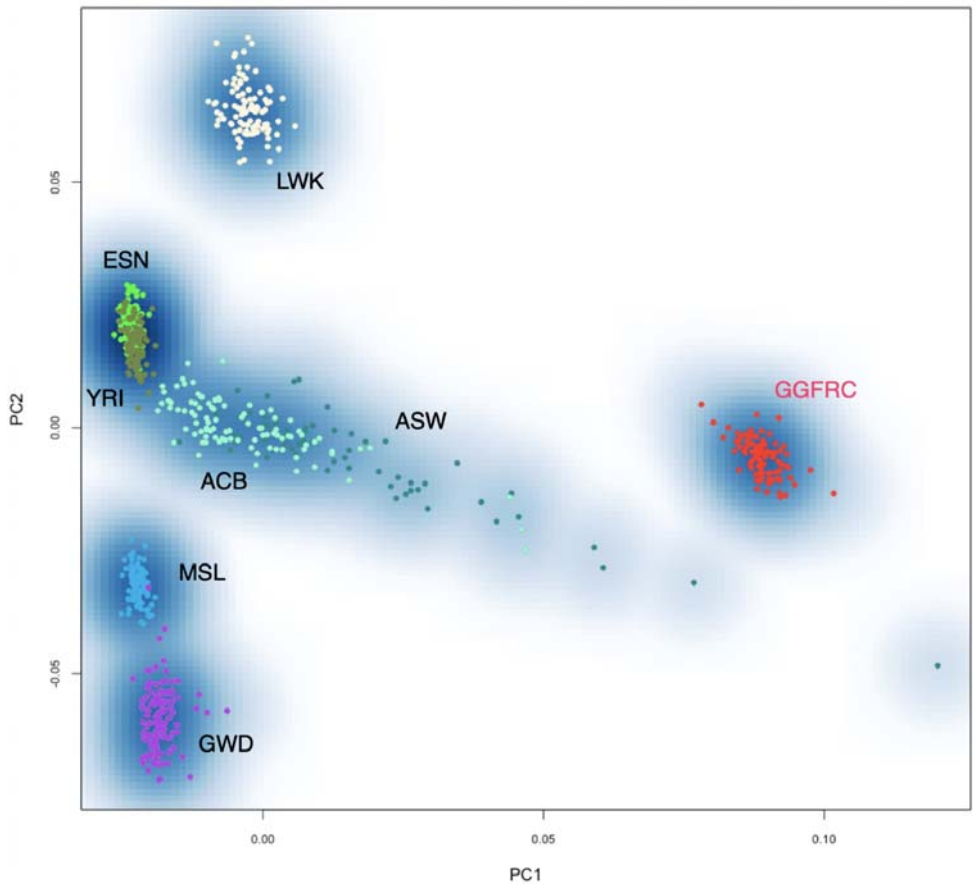
Analyses conducted in Ethiopia: We collected blood samples (10 ml venous blood) during the T1v assessment of the first study reported above. The samples were transported to the study laboratory by a cold chain system preserving the integrity of the sample and stored in refrigerators at 2-8 °C after reaching the laboratory. Subsequently, blood samples were transported to JU and stored in freezers (-80°C). For DNA extraction, we established state-of-the-art procedures on site: DNA was extracted using chemagic DNA Blood 10k Kits (Perkin Elmer).

Analyses conducted in Germany: We tested the quantity and quality of the DNA extracted in laboratories at JU. The purity and homogeneity of the samples was tested by spectrophotometric measurements. For photometric determination of the concentration of DNA, we used Bio Photometer technology with absorbance measured at 260 nm. The samples were genome-wide genotyped using the Infinium Global Screening Array BeadChip (Illumina). This BeadChip includes a multi-ethnic genome-wide content which was selected at minor allele frequencies of > 1% across all 26 1000 Genomes Project populations including cohorts from Africa *(Huang et al., 2011; Ha et al., 2014; Auton et al., 2015).*

Results

The genotyping of all individuals (N=100) in the genetic pilot study was successfully completed with high quality; the overall sample call rate was 99.21%. We followed standard quality control (QC) protocols to process our data, including filters for call rate, deviations from Hardy-Weinberg equilibrium (HWE), and minor allele frequency (MAF). In total, 2.54% (17,765) of the SNPs were removed due to a low call rate (98%), 1.67% (11,401) because of significant deviations from HWE, and 42.19% (283,074) because of a MAF <1%. One person was excluded due to a call rate <98% and three individuals were removed because they were related within the sample (>0.2 estimated in PLINK after additional QC and LD pruning following standard protocols) *(Purcell et al., 2007)*. We found no signs of sample contamination (based on inbreeding coefficients).

We also performed downstream analyses of our GWAS pipeline to further assess the quality and usability of our data. This included a principle component analysis (PCA) using the EIGENSOFT software package (with default parameters) as well as an example GWAS on NE concentration in urine for our study sample *(Li Q et al., 2018)*. For the PCA we merged our data with the 661 African samples from the 1000 Genomes dataset. In line with our expectations and previous reports *(Gallego et al., 2015; Fan et al., 2019)*, samples from GGFRC mapped separately from other African populations in the 1000 genomes dataset (s. Figure 6). For the GWAS of the NE concentration in urine in the quality-controlled, genotyped markers (n=387,836) we used a linear regression (as implemented in PLINK) with PCA components 1-10 as covariates. As expected, our GWAS did not reveal any genome-wide significant association (minimum P-value 3.38 x 10-7; rs56124025 located on chromosome 3; lambda= 1.015).



Legend to Figure 6. ACB: African Caribbean in Barbados (n=96); ASW: Americans of African Ancestry in SW USA (n=61); ESN: Esan in Nigeria (n=99); GWD: Gambian in Western Divisions in the Gambia (n=113); LWK: Luhya in Webuye, Kenya (n=99); MSL: Mende in Sierra Leone (n=85); YRI: Yoruba in Ibadan, Nigeria (n=108); GGFRC: Gilgel Gibe Field Research Center, Southwestern Ethiopia, located 55 km northeast of Jimma City (n=96). PC1: principle component 1; PC2: principle component 2.

Conclusion

Encouraged by the high quality generated during the pilot studies, we are currently preparing the full study with a sample size of N=10,000 to study genetic variation and gene-environment interactions in Ethiopia, especially the relationship of khat abuse with the development of psychotic symptoms and its interactions with genetic factors. The GGFRC offers a unique opportunity to build well-characterized samples and to perform genetic studies that, till date, have not yet been undertaken in Ethiopia at this scale and that will supplement other efforts currently underway in Africa. Moreover, we will be in a unique position to study the relationship between khat use, psychosis, and trauma. The information obtained from this pilot study is instrumental for the preparation of a comprehensive genetic study in a developing African country.

4.3 Proebstl L, Kamp F, Manz K, Krause D, **Adorjan K**, Pogarell O, Koller G, Soyka M, Falkai P, Kambeitz J. Effects of stimulant drug use on the dopaminergic system: A systematic review and meta-analysis of in vivo neuroimaging studies. *Eur Psychiatry.* 2019;59:15-24.

Introduction

Stimulant drugs such as amphetamine, methamphetamine, and cocaine can cause persistent changes in the brain, for example in the striatum. They cause an unbalanced dopaminergic system, which leads to alterations and impairments in the reward system and circuits. This change in the reward system combined with withdrawal symptoms is one reason for symptoms of addiction for the development of psychotic symptoms *(Schultz et al., 1997).* Imaging studies with positron emission tomography (PET) or single photon emission computerized tomography (SPECT) have found differences between stimulant users and healthy controls *(e.g. Simon et al., 2004; dela Peña et al., 2015).* For amphetamines, most studies reported significantly decreased dopamine transporter (DAT) in abstinent heavy users *(Johanson et al., 2006)* and decreased receptor levels in recreational *(Schrantee et al., 2016)* or former users *(Schrantee et al., 2015)* compared to healthy controls. Other studies showed a negative trend *(Schrantee et al., 2016)* or no changes in recreational users *(Schouw et al., 2013)* compared to healthy controls. The aim of this analysis was to examine differences between users and nonusers of stimulating substances and whether these substances differ in their effects on the dopamine system's function in the striatum. Furthermore, here we will discuss the results with regard to the sensitization model of psychosis (s. publication 4.1).

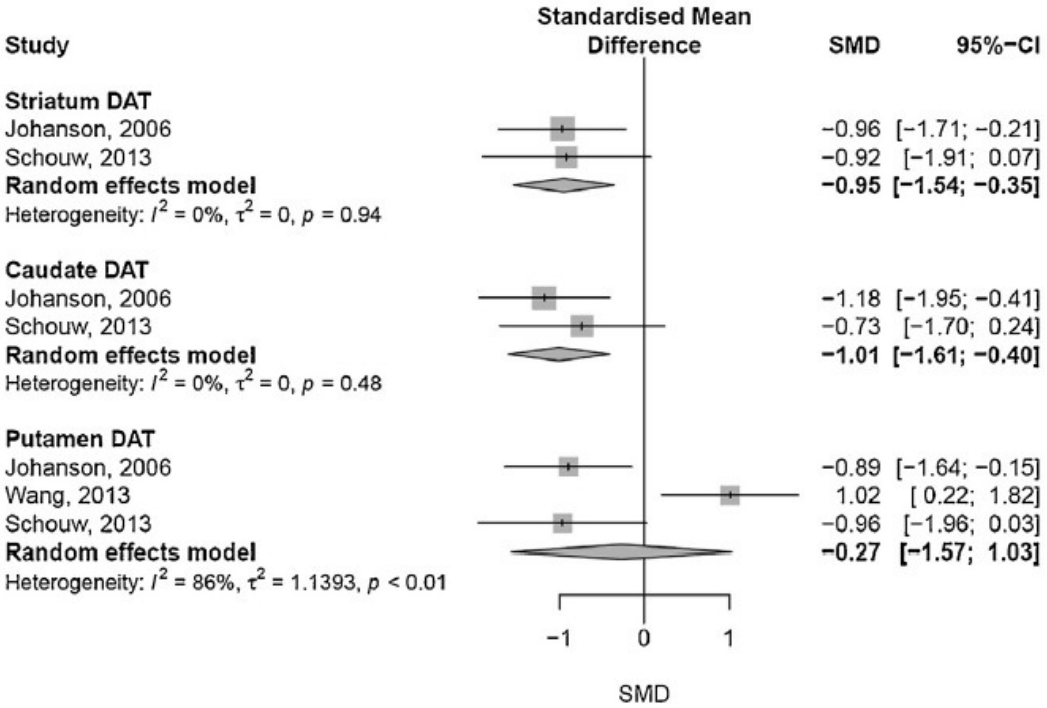
Methods

This study focused on influences of stimulant use on dopaminergic function assessed using nuclear-medicine imaging (PET/SPECT). Included were 39 studies on 655 cocaine, amphetamine, methamphetamine or nicotine users, as well as 690 healthy controls. Meta-analyses were conducted separately for D2/D3 receptors and dopamine transporters of the entire striatum, its subregions caudate and putamen respectively.

Results

Meta-analyses´ results regarding amphetamine users showed reduced DAT availability in the striatum, as well as in the sub regions (s. Figure 7). For DAT availability in the whole striatum, k = 2 studies comprising N = 23 users and N = 26 controls were included. The summarized effect size was significant with g=-0.95 (95% CI: [-1.54, -0.35], p < 0.01). This result indicates a lower DAT availability in the striatum of amphetamine users. When investigating the subregions, k = 2 studies with N = 23 users and N = 26 controls were included for the comparison of DAT availability in the caudate. The summarized effect size was significant with g=-1.01 (95% CI: [-1.61, -0.40] p < 0.01). This result indicates a lower DAT availability in the caudate of amphetamine users. For the analysis of DAT availability in putamen, k = 3 studies were included with N = 41 users and N = 37 controls. The summarized effect size was g=-0.27 (95% CI: [-1.57, 1.03], p = 0.69). There was no evidence for publication bias (p = 0.88), or moderation effects for year of publication (p = 0.58), age (p = 0.69), used method (p = 0.54) and minimal duration of abstinence (p = 0.41). A significant moderation effect for gender was found (p = 0.01), pointing to a stronger negative effect with an increasing ratio of men to the total number of participants.

Figure 7. Forest Plot of meta-analysis of striatal dopaminergic function in amphetamine users vs. non users



Discussion

This meta-analysis provides evidence that there are ongoing changes in the dopaminergic system associated with the use of stimulants. For DAT, the results from the striatum and for the subregion caudate and putamen showed a down-regulation after amphetamine use. The human brain does adapt to changes like these *(Ornstein et al., 2000)*, which might be a reason for cognitive impairments like poorer performance in flexibility and memory tasks or spatial working memory in chronic amphetamine users *(Woicik et al., 2009)* compared to healthy controls. The down regulation process in the striatum might be one reason for craving or even lead to relapses *(Härtel-Petri et al., 2016)* because the endogenous dopamine is no longer enough for sufficient stimulation *(Wang et al., 2013)*. Thus, effects on the dopaminergic system inferred from this analysis may be one reason for addictive behaviors and the development of neurocognitive deficits in stimulant users. In terms of the sensitization theory, even down-regulated striatal D2-receptors can be in a high-affinity state, showing an increased sensitivity to dopamine agonists and a higher reward dependent dopamine release *(Flagel et al., 2011; Weidenauer et al., 2017)* (s. publication 4.1). To conclude, this meta-analysis shows evidence for changes in the striatal dopaminergic system under stimulant use but, it also shows the importance of further neuroimaging research.

4.4 Abdeta T, Tolessa D, **Adorjan K**, Abera M. Prevalence, withdrawal symptoms and associated factors of khat chewing among students at Jimma University in Ethiopia. *BMC Psychiatry.* 2017; (17):142.

Introduction

Another important aspect of khat consumption is the development of withdrawal symptoms. Recently, khat chewing has become a common practice among high school, college, and university students for recreational purposes and because they believe that it increases their academic performance *(Hussain, 2013; Wakgari et al., 2011)*. Khat chewers spend long hours chewing and then recovering from it, which can lead to a loss of work hours and absenteeism from work and classes and potentially result in a decrease in overall national economic productivity and poor academic performance among students *(WHO 2006; Hussain, 2013)*. The available literature is inconsistent regarding the presence or absence of khat withdrawal symptoms. One study on the pharmacological and medical aspects of khat and its social use in Yemen found that when chronic khat chewers stop chewing, they develop withdrawal symptoms such as feeling hot in their legs, nightmares, mild depression, slight tremor, lethargy, a desire to chew khat, and so on *(Al-Motarreb et al., 2002)*. However, another study on substance abuse in outpatients attending rural and urban health centers in Kenya found no signs of khat dependency or withdrawal symptoms *(Othieno et al., 2000)*. No research was available on the prevalence, withdrawal symptoms, and associated factors of khat chewing in our study area, and we found no study on khat withdrawal symptoms in other regions of Ethiopia. Therefore, the objective of this study was to determine the prevalence, withdrawal symptoms, and associated factors of khat chewing among regular undergraduate students of the main campus at JU to provide additional information on the prevalence of khat chewing and khat withdrawal symptoms.

Methods

The institution-based, cross-sectional study was conducted in January 2016 among 651 regular undergraduate students of the main campus at JU. A self-administered, structured questionnaire adapted from the literature was used. The questionnaire had three parts: (I) socio-demographic information; (II) khat chewing habits and substance use other than khat; and (III) checklist to assess khat withdrawal symptoms. Collected data were checked for completeness, coded, entered into Epidata 3.1 and then exported to SPSS version 20 for Windows for statistical analysis. Bi-

variate and multivariate logistic regressions were used to explore the presence of associations and identify independent predictors of khat chewing. Variables with a p-value <0.25 in the bivariate analysis were entered into multivariate logistic regressions in order to control for potential confounders and calculate adjusted odds ratios with a 95% confidence interval (95% CI). Variables with $p < 0.05$ in the multivariate logistic regressions were considered as significantly associated with khat chewing.

Results

The study found that the lifetime and current prevalence of khat chewing among students were 26.3% (95% CI: 24.3, 28.3) and 23.9% (95% CI: 21.94, 25.86), respectively. About 25.7% of students started chewing after joining university, and 60.5% of these students started during their first year. The main reason given for starting khat chewing was for study purposes (54.6%), followed by socialization purposes (42.3%) (s. Figure 8). Among current khat chewers, 72.9% reported that they had chewed khat for 1 year or more and 68.2% reported that they had experienced various withdrawal symptoms. The most frequently reported withdrawal symptoms were feeling depressed, craving, and feeling fatigued (s. Figure 9). Male gender, attending a place of worship daily/2–3 times per week, cannabis use, smoking cigarettes, and having family members currently chewing khat were independently associated with khat chewing.

Figure 8. Reasons for starting khat chewing among undergraduate students at JU

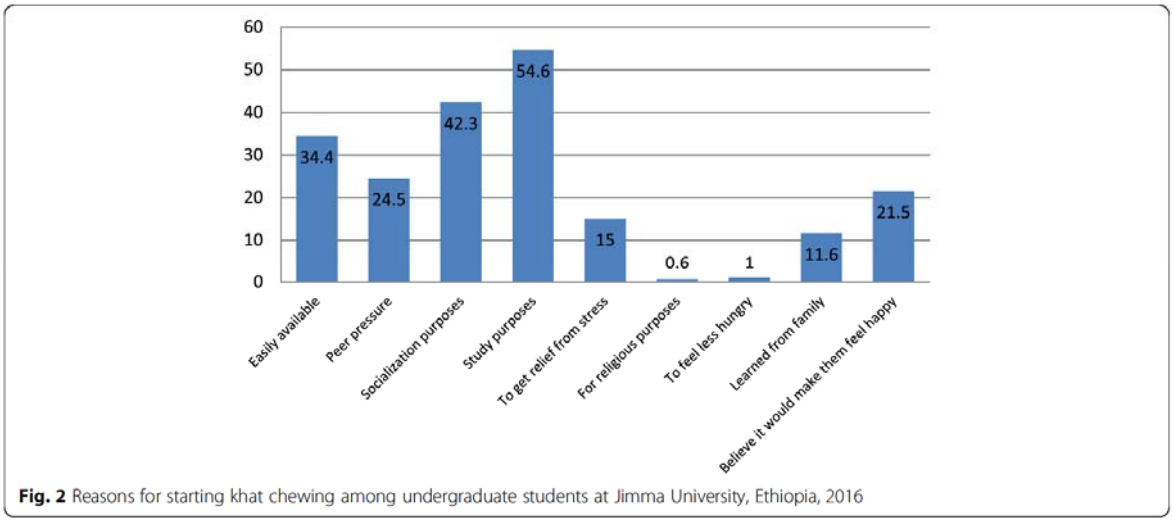


Fig. 2 Reasons for starting khat chewing among undergraduate students at Jimma University, Ethiopia, 2016

Figure 9. Withdrawal symptoms reported among undergraduate students at JU

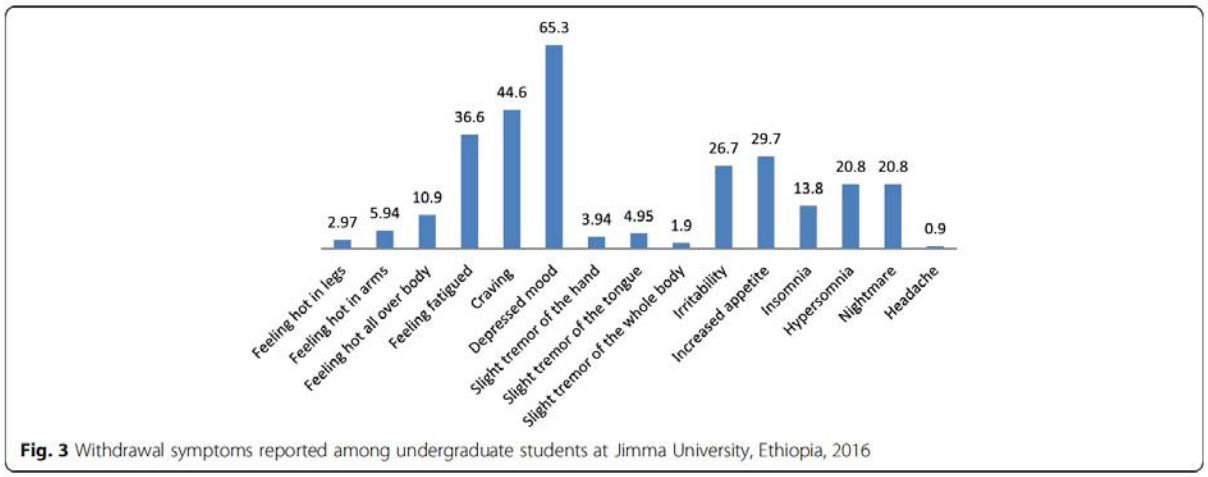


Fig. 3 Withdrawal symptoms reported among undergraduate students at Jimma University, Ethiopia, 2016

In addition, we found that the following independent variables are significantly associated with khat chewing: male gender, attending a place of worship daily/2–3 times per week, current use of ganja/cannabis, current smoking cigarettes and having family members who are current khat chewers. Students who had used cannabis at least once during the last month had more than four times higher odds of chewing khat than those who did not use it during the last month (AOR 4.17, 95% CI: 1.6, 11.2) (s. Table 4).

Table 4. Substance use other than khat and school related factors independently associated with current khat chewing among undergraduate students at JU

Variables	Current khat chewing		*P*-value	AOR (95% CI)
	Yes	No		
Cumulative grade point average (cGPA)				
< 3.25 (less than distinction level)	67 (28.2)	171 (71.8)	Reference	Reference
≥ 3.25 (distinction level)	50 (21.8)	179 (78.2)	0.38	0.82 [0.53–1.27]
Alcohol used at least once during the last 1 month				
No	82 (19.2)	345 (80.8)	Reference	Reference
Yes	66 (34.4)	126 (65.6)	0.53	1.15 [0.7–1.8]
Smoking cigarettes at least once during the last 1 month				
No	89 (18.5)	392 (81.5)	0.001	0.45 [0.3–0.7]
Yes	59 (42.8)	79 (57.2)	Reference	Reference
Ganja/cannabis used at least once during the last 1 month				
No	134 (22.4)	463 (77.6)	Reference	Reference
Yes	14 (63.6)	8 (36.4)	0.004	4.17 [1.6–11.2]
Shisha used at least once during the last 1 month				
No	129 (24)	408 (76)	Reference	Reference
Yes	19 (23.2)	63 (76.8)	0.9	1.02 [0.51–2.06]

Discussion

This study found that large numbers of university students chew khat; this is in line with that found among students at Jazan University, Saudi Arabia (23.1%) *(Rashad et al., 2013)* and at Haramaya University, Ethiopia (23.6%) *(Tesfaye et al., 2014)*. However, the prevalence is higher than that found at Addis Ababa University and Gondar University and at four other colleges in North West Ethiopia *(Dachew et al., 2015; Kebede et al., 2002)*. The study gave new ideas regarding khat withdrawal symptoms in Ethiopia: The most frequently reported withdrawal symptoms were feeling depressed, craving, and feeling fatigued. This finding is comparable also to DSM-5 stimulant withdrawal diagnostic criterion "B," which specifies that dysphoric mood and two or more of the following physiological changes (fatigue, unpleasant dreams, insomnia or hypersomnia, increased appetite, and psychomotor retardation or agitation) should occur within a few hours to several days *(Sadock et al., 2015)*. Factors significantly associated with khat chewing were male gender, attending a place of worship daily/2– 3 times per week, currently using ganja/cannabis, current smoking cigarettes and having family members who chew khat. This finding shows that poly-substance use behavior can be found among students with a khat chewing habit. They serve as a critical role of providing information to form rational foundation for public health policy, prevention and planning to bring change in contributing factors for khat chewing.

4.5 Yitayih Y, Abera M, Eliais Tesfaye E, Mamru A, Soboka M, **Adorjan K.** Substance use disorder and associated factors among prisoners in a correctional institution in Jimma, Southwest Ethiopia: a cross-sectional study. *BMC Psychiatry.* 2019;18(1):314.

Introduction

Another important aspect of khat consumption is the examination of consumer behaviour among specific populations such as prisoners. In this context we conducted three studies: 1) with a focus on substance use, 2) on trauma, and 3) on psychopathy. These findings will be presented next.

Substance use and criminal behavior are closely related, and a large proportion of substance users commit crimes while under the influence of a substance *(National Council on Alcoholism and Drug Dependence, 2018)*. According to a U.S. Department of Justice report, in 2004 about one-third (32%) of inmates in state facilities reported that they had committed a crime while under the influence of drugs *(Mumola et al., 2006)*. Alcohol is a factor in 40% of all violent crimes in the USA *(National Council on Alcoholism and Drug Dependence, 2018)*, and alcohol and other drugs contribute to 78% of violent crimes, 83% of property crimes, and 77% of public order crimes *(The National Center on Addiction and Substance Abuse at Colombia University, 2018)*. Inmates with substance abuse problems are more likely to be re-incarcerated, begin their criminal careers at an early age and have more contact with the criminal justice system. Additionally, prisoners with substance abuse problems are four times more likely to receive income through illegal activities *(The National Center on Addiction and Substance Abuse at Colombia University)*. Despite the contribution of substance use disorder to the global burden of diseases and the high prevalence among incarcerated people, little attention is given to this disorder in the general population and among prisoners in particular *(Rounds-Bryant et al., 2007)*. This is particularly true in low-income countries; in Ethiopia, for example, no study has ever examined the prevalence of substance use disorder in a prison population. Therefore, this study aimed to assess the prevalence of this disorder and associated factors among prisoners in a correctional institution in Jimma, Southwest Ethiopia.

Methods

We used a cross-sectional study design to collect data from 336 prisoners from June 5 to July 5, 2017 in the correctional institution in Jimma. Study participants were selected from the total of 1460 prisoners eligible for the study by a systematic random sampling technique, i.e., one participant was randomly selected from every four consecutive admissions in the registration book. Alcohol use disorder (AUDIT), nicotine dependence (FTND), khat abuse (DAST), cannabis use disorder (CUPIT), psychopathy (Psychopathy Checklist), adverse traumatic life events (LEC-5), and social support (Oslo 3-item Social Support Scale) were assessed. Data were entered into EpiData version 3.1 and analyzed in bivariate and multivariable logistic regression models with the Statistical Package for Social Science version 21. Variables with a P value < 0.05 in the final fitting model were declared to be associated with the outcome variable.

Results

A total of n = 227 (69.0%) of the participants had a history of substance use. The overall prevalence of substance use disorder was 55.9% and reported a substance use disorder within the 12 months before imprisonment. The prevalence of khat abuse was 41.9%; alcohol use disorder, 36.2%; nicotine dependence, 19.8%; and cannabis use disorder, 3.6%. A total of n = 105 participants (31.9%) had a history of two or more substance use disorders. The median age at the first use of a substance was 16 years (IQR 5), and 44% of the participants started using the substance before the age of 15 years. The median duration of substance use was 6 years. The main reasons for starting substance use reported by participants were peer pressure (41.8%), recreational reasons (34.2%), and stress relief (29.3%). Almost all of the prisoners with a substance use disorder had not received treatment prior to imprisonment (96.7%), but 66.3% of them were interested in receiving treatment (s. Table 5). A third (33.7%), however, wanted to continue using the substance after they were released from prison. The median age of participants at the first imprisonment was 24 years. Assault and murder were the most common causes of imprisonment. Most of the participants had no previous history of imprisonment, and most of the crimes were not committed under the influence of a substance. Among the crimes that were committed under the influence of a substance (n = 42/329), n = 24 (57.1%) were committed under the influence of alcohol; n = 14 (33.3%), under the influence of khat; and n = 4 (9.6%), under the influence of cannabis.

Table 5. Forensic history of prisoners in the correctional institution in Jimma

Variables		Frequency	Percentage (%)	Substance use disorder	
				No, *n* (%)	Yes, *n* (%)
Reason for admission to prison	On remand	25	7.6	15 (60.0)	10 (40.0)
	Convicted	304	92.4	130 (42.8)	174 (57.2)
Type of offence committed	Assault	103	31.3	38 (36.9)	65 (63.1)
	Murder	83	25.2	41 (49.4)	42 (50.6)
	Theft	81	24.6	34 (42.0)	47 (58.0)
	Rape	32	9.7	16 (50.0)	16 (50.0)
	Robbery	12	3.6	5 (41.7)	7 (58.3)
	Other[a]	18	5.4	11 (61.1)	7 (38.9)
Previous imprisonment	No	301	91.5	140 (46.5)	161 (53.5)
	Yes	28	8.5	5 (17.9)	23 (82.1)
Committed crime under the influence of substance	No	287	87.2	140 (48.4)	147 (51.6)
	Yes	42	12.8	5 (11.9)	37 (88.1)

[a]Other types of offence = political offence and offence related to forest destruction

Multivariable logistic regression showed that four variables were significantly associated with substance use disorder: poor social support (adjusted odds ratio [AOR]: 4.41; 95% CI, 2.22–8.77), living in an urban setting (AOR: 2.42; 95% CI, 1.33–4.40), psychopathy (AOR: 4.68; 95% CI, 1.71–12.78), and a family history of substance use (AOR: 4.39; 95% CI, 2.49–7.79). Prisoners with poor social support were more than four times more likely to develop a substance use disorder than prisoners with good social support (AOR:4.41; 95% CI, 2.22–8.77). Also, prisoners living in an urban setting were more than two times more likely to have a substance use disorder than prisoners living in a rural setting (AOR:2.42; 95% CI, 1.33–4.40). Prisoners with psychopathy were nearly five times more likely to develop a substance use disorder than those without psychopathy (AOR: 4.68; 95% CI, 1.71–12.78). Prisoners with a family history of substance use were more than four times more likely to have a substance use disorder than prisoners with no family history of substance use (AOR: 4.39; 95% CI, 2.49–7.79) (s. Table 6).

Table 6. Multivariable logistic regression analysis for independent predictors of a substance use disorder among prisoners (n = 329) in a correctional institution in Jimma

Variable		Substance use disorder		AOR (95% CI)
		No, *n* (%)	Yes, *n* (%)	
Social support	Poor support	53 (28.8)	131 (71.2)	4.41 (2.22–8.77)
	Moderate support	48 (63.2)	28 (36.8)	1.07 (0.49–2.34)
	Strong support	44 (63.8)	25 (36.2)	Reference value
Family history of substance use	No	110 (57.0)	83 (43.0)	Reference value
	Yes	35 (25.7)	101 (74.3)	4.39 (2.49–7.79)
Psychopathy	No	139 (48.3)	149 (51.7)	Reference value
	Yes	6 (14.6)	35 (85.4)	4.68 (1.71–12.78)
Place of residence	Rural	60 (56.6)	46 (43.4)	Reference value
	Urban	85 (38.1)	138 (61.9)	2.42 (1.33–4.40)

Discussion

Substance use disorder is highly prevalent among prisoners. Our finding that just over half of all prisoners had a substance use disorder within 12 months prior to their imprisonment is alarming since substance use disorder treatment is not accessible in the prison. If current prevalence rates are generalizable to all prisons in Ethiopia, our results suggest that about two thirds of prisoners with substance use disorder are interested in receiving treatment; however, almost no prisoners with substance use disorder have access to such treatment services. Research has shown that an unfortunate consequence of this shortage of treatment services is that offenders quickly return to drug use and crime after their release from prison *(Kinner et al., 2006; Thomas et al., 2014)*. With regard to the treatment of substance use disorder in prison, therapeutic community intervention (TCI) and individual and group therapy are methods that can decrease the rates of re-incarceration, drug misuse relapse, and re-arrest *(Belenko et al., 1998)*. This study has substantial clinical implications for health services in correctional institutions because it shows the need for management plans for acute substance withdrawal and for recovery and rehabilitation support for prisoners with substance use disorder.

4.6 Yitayih Y, Abera M, Eliais Tesfaye E, Mamru A, Soboka M and **Adorjan K.** Trauma exposure and alcohol use disorder among prisoners in a correctional institution in Jimma, Southwest Ethiopia: Across-sectional study. *BMC Res Notes.* 2019;19;12(1):748.

Introduction

Traumatic events are an almost universal experience among prisoners *(Carlson et al., 2010)*. One study found trauma exposure rates ranging from 62.4 to 87.0% among incarcerated adult males *(Gibson et al., 1999)*. Another study showed that 22% to 43% of patients with posttraumatic stress disorder (PTSD) develop a substance use disorder over the course of their lives *(Jacobsen et al., 2001)*. Studies have identified several potential mechanisms such as the behavioral sensitization paradigm *(Robinson et al., 2015),* the self-medication hypothesis *(Khantzian, 1986),* and the high-risk hypothesis *(Cottler et al., 1992)* to explain the relationship between trauma exposure and substance use disorders (s. publication 4.1). The vulnerability may be influenced by a lack of coping strategies or neurochemical brain changes caused by substance use *(Brown et al., 1994)*. However, to our knowledge the potential association of traumatic life events with problematic alcohol use has not been examined among prison populations in Ethiopia. Therefore, this study aimed to assess trauma exposure and AUD in prisoners in the aforementioned correctional institution in Jimma.

Methods

We conducted a cross-sectional study in the correctional institution in Jimma over a 4-week period (June–July) in 2017. We assessed the presence of AUDs with the Alcohol Use Disorders Identification Test (AUDIT). Adverse traumatic life events were evaluated with the Life Events Checklist (LEC). We assessed nicotine dependence by the Fagerstrom Test for Nicotine Dependence (FTND). To evaluate khat abuse we used the Drug Abuse Screening Test (DAST). In addition, we used a questionnaire to assess the following variables for AUD: socioeconomic factors (age, sex, marital status, ethnicity, religion, educational status, occupation, income); environmental factors and behavioral and mental health factors. We assessed social support with the Oslo 3-item Social Support Scale and psychopathy with the Psychopathy Checklist (see above). The data were exported to the Statistical Package for Social Science version 21.0 for further analysis, and binary logistic regression analysis was used for both bivariate and multivariate analysis to explore associations and identify variables independently associated with AUD. Factors associated

with the outcome variables that had a P value < 0.25 in the bivariate analysis were included in the multivariable analysis. Statistical significance was set at P < 0.05.

Results

A total of 329 prisoners participated in the study. The median age of the participants was 26 years. Of the 329 participants, 209 (63.5%) had lifetime trauma exposure and 132 (40.1%) had AUD. Of the 209 prisoners with lifetime trauma exposure, 92 (44.0%) had AUD in the 12 months before imprisonment: 44 (21.1%) had hazardous drinking, 16 (7.7%) had harmful drinking, and 32 (15.8%) had alcohol dependence; 117 (56%) had no alcohol use problem. The most commonly encountered types of trauma in the whole group and in the prisoners with AUD were transportation accidents (whole group: n = 126, 38.3%; prisoners with AUD: n = 69, 54.8%) and physical assault (whole group: n = 91, 27.7%; prisoners with AUD: n = 64, 70.3%). In the whole group, 146 (44.4%) participants had experienced two and more traumatic events. Among the prisoners with AUD (n = 119), 27 (22.7%) had no exposure to a traumatic life event, 23 (19.3%) had experienced one traumatic life event, and 69 (58%) had experienced multiple traumatic life events.

Multivariable logistic regression showed that experiencing multiple traumatic life events was significantly associated with AUD: Prisoners who had experienced multiple traumatic life events were almost three times more likely to develop AUD than prisoners with no exposure to a traumatic life event (adjusted odds ratio 2.47, 95% CI:1.23, 4.94) (s. Table 7).

Table 7. Multivariable logistic regression analysis for independent predictors of alcohol use disorder among prisoners in a correctional institution in Jimma

Variable	Alcohol use disorder		AOR (95% CI)
	No (%)	Yes (%)	
Psychopathy			
No	200 (69.4)	88 (30.6)	Reference value
Yes	10 (24.4)	31 (75.6)	3.33 (1.25– 8.86)
Adverse traumatic life event			
No exposure to traumatic life event	93 (77.5)	27 (22.5)	Reference value
Exposure to one traumatic life event	40 (63.5)	23 (36.5)	2.04 (0.86–4.88)
Exposure to multiple traumatic life events	77 (52.7)	69 (47.3)	2.47 (1.23–4.94)
Place of residence			
Rural	89 (84.0)	17 (16.0)	Reference value
Urban	121 (54.3)	102 (45.7)	4.86 (2.38–9.94)
Khat abuse			
No	159 (83.2)	32 (16.8)	Reference value
Yes	51 (37.0)	87 (63.0)	7.39 (3.99–13.68)
Nicotine dependence			
No	186 (70.5)	78 (29.5)	Reference value
Yes	24 (36.9)	41 (63.1)	2.49 (1.16–5.34)

AOR adjusted odds ratio, *95% CI* 95% confidence interval

Reference value: In the analysis, this variable indicated a lower likelihood of alcohol use disorder; it was coded as zero in SPSS logistic regression

Discussion

We found that prisoners with trauma exposure were at greater risk for AUD than prisoners with no trauma exposure: 92 (44.0%) of the prisoners with lifetime trauma exposure had an AUD in the 12 months before imprisonment, compared with 27 (22.5%) of the prisoners without lifetime trauma exposure. Participants who had been exposed to multiple traumatic life events had higher odds of association for AUD than participants with no exposure to traumatic life events. In the present study, the group of people who consumed alcohol was also the group with the highest trauma load. Thus, we can assume that the prevalence of PTSD was very high among these respondents and that they intentionally used substances to better deal with symptoms from the PTSD spectrum, according to the self-medication hypothesis *(Khantzian, 1986)*. Although we cannot establish clear causality from our data, mental health professionals should recognize that multiple traumatic exposures among prisoners may be a particular risk factor for AUD.

4.7 Yitayih Y, Soboka M, Tesfaye E, Abera M, Mamaru A, **Adorjan K.** A cross-sectional study of psychopathy and khat abuse among prisoners in the correctional institution in Jimma, Ethiopia. *PLoS One. 2020;*15(1).

Introduction

Psychopathic personality is an important construct that has been linked to criminal behavior and problematic substance use, and substance use greatly increases the likelihood that psychopathic individuals will engage in serious or violent criminal activity *(Steadman et al., 2000)*. Indeed, a large-scale study on aggression and offending found that the best predictor of violence was psychopathic traits in conjunction with substance use *(Steadman et al., 2000)*. Also khat abuse and psychopathy are both strongly related to criminal activity (s. publication 4.5). Higher rates of substance use in people with psychopathy are hypothesized to be related to psychopathic personality traits, which include high sensation seeking, low conscientiousness and neuroticism, impulsivity, and irresponsibility *(Leistico et al., 2008)*. Little is known, however, about the association between psychopathy and khat abuse among prisoners in Ethiopia. Therefore, we evaluated the presence of these two factors in prisoners in the aforementioned correctional institution in Jimma.

Methods

We conducted a cross-sectional study in the correctional institution in Jimma, from June 5 to July 5, 2017. We assessed khat abuse with the Drug Abuse Screening Test (DAST), a 10-item, self-administered questionnaire. Psychopathy was measured with the Psychopathy Checklist: Screening Version (PCL: SV). In addition to examining psychopathy and khat abuse, we assessed the presence of alcohol use disorders (AUDs) as well as adverse traumatic life events with the Life Events Checklist (LEC). Nicotine dependence was assessed by the Fagerstrom Test for Nicotine Dependence. We also determined social support with the Oslo 3-item Social Support Scale. Finally, we used a questionnaire to evaluate the following potential explanatory variables for substance use disorder: socioeconomic factors (age, sex, marital status, ethnicity, religion, educational status, occupation, income); environmental factors (family history of substance use, social support, immigration history); behavioral and mental health factors (previous known mental illness, perception that substance use does not impair health, start of substance use at an early age, chronic physical illness, suicidal ideation and attempts); and criminal factors (previous arrests, previous substance-related offences, type of crime, committed a crime under the influence of a substance).

After the tests and questionnaires had been checked for completeness, data were entered into EpiData Version 3.1 and then exported to the Statistical Package for Social Science version 21.0 for further analysis. Descriptive statistics, such as frequencies and medians, were computed, and bivariate and multivariable analyses were used to identify factors associated with the outcome variables. All variables associated with khat abuse in the bivariate logistic regression with a P value < 0.25 were entered together into the multivariable logistic regression by default (enter method) to control for potential confounders. Variables with P value < 0.05 were declared to be associated with khat abuse in the final model. An odds ratio with a 95% confidence interval (95% CI) was calculated to assess the level of association and statistical significance.

Results

A total of 329 prisoners participated in the study. Possible psychopathy was present in 26/329 participants (7.9%; PCL: SV score . 13 but < 18); and probable psychopathy, in 15/329 (4.6%; PCL: SV score .18). Psychopathy symptoms are glib and superficial charm, grandiose self-worth, pathological lying, lack of remorse or guilt, callousness and lack of empathy, early behavior problems, lack of realistic long-term goals, impulsivity, irresponsibility, failure to accept responsibility for own actions, juvenile delinquency and adult anti-social. In the total sample, the prevalence of lifetime khat use was 197/329 (59.9%); and of khat abuse, 138/329 (41.9%). Among the participants with possible or probable psychopathy, 32/41 (78.0%) had a history of khat abuse, and among prisoners with khat abuse, 21/ 138 (15.2%) had possible psychopathy and 11/138 (8.0%) had probable psychopathy. The most common psychopathic traits were pathological liar (18/138; 13.0%) and a history of juvenile delinquency (14/138; 10.1%). The most common crimes among prisoners with possible or probable psychopathy were murder 13/41 (31.7%) and assault 13/41 (31.7%) (s. Table 8).

Table 8. Types of crime committed by prisoners with psychopathy in the correctional institution in Jimma

Type of offence	Psychopathy	
	No (%)	Yes (%)
Robbery	12 (4.2)	3 (7.3)
Rape	29 (10.1)	3 (7.3)
Murder	70 (24.3)	13(31.7)
Theft	73 (25.3)	8 (19.5)
Assault	90 (31.3)	13 (31.7)
Others*	14 (4.9)	1 (2.5)
Total	288 (100)	41 (100)

* Political offence or offence related to forest destruction

The bivariate analysis found that various socio-demographic, behavioral, mental health, environmental, and criminal factors were associated with khat abuse, as follows: male sex (crude odds ratio [COR]: 2.01; 95% CI: 0.77, 5.128; p = 0.156), living in an urban setting (COR: 1.64; 95% CI: 1.01, 2.65), p = 0.044), psychopathy, multiple traumatic life events, suicidal ideation and suicide attempts, family history of substance use, poor social support, immigration history, and previous history of imprisonment. These variables were included in the multivariable analysis. The multivariable analysis indicated that the following variables were associated with higher odds of having khat abuse: psychopathy, family history of substance use, poor social support, AUD, and suicidal ideation and suicide attempts (s. Table 9).

Table 9. Multivariable logistic regression analysis of independent predictors of khat abuse among prisoners in the correctional institution in Jimma

Variable		Khat abuse		AOR (95% CI)
		No (%)	Yes (%)	
Psychopathy	No	182 (63.2)	106 (36.8)	Reference value
	Yes	9 (22.0)	32 (78.0)	3.00 (1.17–7.67)
Social support	Poor support	112 (60.9)	72 (39.1)	2.28 (1.11–4.67)
	Moderate support	49 (64.5)	27 (35.5)	0.61 (0.25–1.52)
	Strong support	49 (71.0)	20 (29.0)	Reference value
Family history of substance use	No	135 (69.9)	58 (30.1)	Reference value
	Yes	75 (55.1)	61 (44.9)	2.50 (1.45–4.31)
Suicidal ideation and suicide attempts	No	152 (62.6)	91 (37.4)	Reference value
	Yes	39 (45.3)	47 (54.7)	2.26 (1.23–4.17)
Alcohol use disorder	No	159 (75.7)	51 (24.3)	Reference value
	Yes	32 (26.9)	87 (73.1)	7.78 (4.16–14.53)

AOR: adjusted odds ratio; 95% CI: 95% confidence interval
Reference value: In the analysis, this variable indicated a lower likelihood of khat abuse; coded as zero in SPSS logistic regression

Discussion

In this study, we assessed the co-morbidity of psychopathy and khat abuse among prisoners in the correctional institution in Jimma. We found that the prevalence of khat abuse in the 12 months before imprisonment was higher in prisoners with possible or probable psychopathy than in those with no psychopathy. Psychopathy was one of the factors significantly associated with khat abuse in this study, and participants with possible or probable psychopathy had three times higher odds of khat abuse than those with no psychopathy. A family history of substance use, poor social support, AUD, and suicidal ideation and suicide attempts were also associated with khat abuse. This finding is in line with a study performed in England and Wales, which found that psychopathy is an important factor for substance use *(Coid J et al., 2009)*. Our findings have implications both for future research on the etiology of offending among people who abuse khat and have AUD and

for recognizing ways to prevent offending in this group. The presence from an early age of behavioral problems can escalate into delinquency, criminality, and substance use. We hypothesize that among life-course–persistent offenders, the antecedents of psychopathic traits emerge very early in life. In addition, the study highlights the need to strengthen addiction health services in the correctional institution in Jimma and to design and implement long-term management plans for recovery and rehabilitation from khat abuse. There was a high prevalence of traumatic life event exposure among the prisoners in this study, so we recommend that researchers evaluate prisoners for posttraumatic stress disorder (s. publication 4.6).

5. SUMMARY

Several potential mechanisms may explain the observed findings of our studies. The most apparent is that psychotic experiences might be a severity marker of mental health problems and that higher khat use and greater experience of traumatic events characterize people with more severe mental health problems. The self-medication hypothesis *(Boys et al., 2003; Khantzian, 1985; Waldrop et al., 2007)* proposes that individuals with more traumatic experiences may use higher amounts of substances to alleviate trauma-related psychiatric symptoms, in which case higher khat use would fit with the higher rate of psychotic experiences. However, this hypothesis does not explain for example the results of our main study (s. publication 4.1), because participants with a positive amphetamine test used the same amount of khat irrespective of the number of experienced traumatic events. However, possible evidence for the self-mediation hypothesis was found in the sub-population of prisoners with AUD and trauma (s. publication 4.6). The trauma hypothesis *(Brady et al., 1998; Coffey et al., 2006; Daly, 2000; Jacobsen et al., 2001; Redman et al., 2017),* i.e. individuals with traumatic experiences are at higher risk to develop psychotic symptoms, also fails to explain our results in our main study (s. publication 4.1) because trauma was not associated with the prevalence of psychotic experiences among participants with a negative khat test. Future studies need to clarify the association between psychotic experiences and specific types of traumatic events, e.g. adverse childhood experiences, which were found in other studies to influence psychotic symptoms *(Alemany et al., 2011)*.

Our findings in the main study (s. publication 4.1) are more in line with the explanation that individuals with a high trauma load are sensitized to the psychotomimetic effects of khat use, i.e. with the behavioral sensitization paradigm and the sensitization model of psychosis *(Howes et al., 2009; Robinson et al., 2015)*. The behavioral sensitization paradigm states that repeated administration of amphetamines or exposure to severe stress can cause a sensitization of dopamine neurons, which subsequently release higher amounts of dopamine in response to stress and amphetamine use *(Robinson et al., 2015; Vanderschuren et al., 2000).* Sensitization of dopaminergic neurons is thought to be involved in the development of positive psychotic symptoms and recurrence of psychotic episodes *(Robinson et al., 2015)* (s. 4.3). The role of the stress x substance use interaction as combined environmental risk factors in the sensitization model of psychosis has rarely been studied in humans. *Yui et al., (2002)* showed that exposure to stress can provoke re-emergence of psychotic symptoms in prisoners with a history of amphetamine-induced psychosis. In longitudinal and cross-sectional studies, childhood traumatic experiences and later tetrahydro-

cannabinol use increased the risk of later reporting psychotic symptoms *(Konings et al., 2012)* or developing psychotic disorders *(Houston et al., 2008)*. Support for the sensitization hypothesis also comes from studies on psychotic symptoms and disorders in specific khat user groups exposed to stress. For example, in a sample of 8,124 active Somali militia members the percentage of respondents with psychotic symptoms increased with the amount of khat used, and this association was much stronger in respondents with that in those without PTSD *(Odenwald et al., 2005)*. In another Somali study in patients with chronic psychosis, age of onset of psychosis was related to age of onset of khat use, and increased khat use was related to higher lifetime trauma exposure; matched healthy controls showed no such relation *(Murray et al., 2013)*. Future studies should specifically test the two potentially meaningful explanatory hypotheses against each other, i.e. khat-induced psychotic experiences are markers of more severe mental health or the consequences of a potential sensitization effect.

Our studies potentially add several new aspects to the scientific discussion on the sensitization hypothesis. First, we found that in the general Ethiopian male population, and not only in a specific subgroup that might be especially prone to substance abuse, the interaction of the environmental risk factors khat and trauma might act on the development of psychotic experiences similar to the interaction of cannabis and trauma *(Konings et al., 2012)*. Second, traumatic experiences-related sensitization to psychotomimetic effects of substances might involve experiences from the whole lifetime and not be limited to childhood experiences. Third, changes in khat availability might influence the presentation of khat-induced psychotic experiences, and the sensitization effect might appear to be larger in the rainy season, when khat is readily available. These findings raise the hope that the mechanisms underlying the onset of psychotic symptoms and disorders can be further studied and better understood by gene x environment studies in humans in countries where khat use is highly prevalent and specific environmental factors (exposure to stress and central stimulant agents) are present. Future studies that further confirm the hypotheses generated from this study should include different perspectives though. For example, population-based genetico-epidemiological studies should examine gene-environment interactions as well as the development and evaluation of integrated (i.e. focusing on several comorbid conditions) and multisectorial (i.e. medical, public health) interventions.

These studies also showed the great need to further explore khat use and its mental health consequences because khat-related harms, such as the still unrecognized risk to develop severe mental disorders, might currently not be correctly classified *(Nutt et al., 2010)*. Exposure to environmental stressors, such as food insecurity, violence, and lack of medical care, is high in the low-in-

come countries around the Horn of Africa where khat use is prevalent. These high levels of stress exposure and khat use and the high prevalence of psychosis in disadvantaged populations call for adequate prevention and treatment tools. Furthermore, the complex associations between these factors might demand the further development of currently available approaches, such as the WHO's mhGAP intervention guide for mental, neurological, and substance use disorders in non-specialized health settings *(WHO, 2013)*.

The undoubted strengths of our studies were the repeated cross-sectional assessments of the same cohorts, which allowed us to examine associations and consider seasonal effects on consumer behavior. In addition, these were one of the first studies with a repeated measurement design to examine khat use in the context of trauma history. Moreover, the studies assessed a representative cross-sectional cohort in an understudied population (African population, sub-population of prisoners).

Our studies also revealed some limitations. First, we did not assess clinical disorders, e.g. PTSD, and did not evaluate psychotic symptoms and disorders as an outcome variable. Future studies must include psychotic symptoms and disorders as an outcome variable to detect the potentially hazardous effects of the studied environmental factors. Second, the screening methods had only moderate sensitivities; however, the high specificities enabled us to study our hypotheses. The immunoassay test in particular measured high khat use rather than any khat use; this was especially evident in the rainy season, when users tended to chew for more hours/week but without exceeding the test's detection threshold. Future studies should use better screening tools. Furthermore, it would be interesting to evaluate whether participants with PTSD intentionally use khat to ameliorate symptoms (self-medication hypothesis s. publication 4.6). In addition, we did not include diagnostic measures that could help determine whether participants had khat use disorders and did not collect additional data on psychotic disorders and other mental health problems. We also need much higher case numbers to study the genetic effect of khat use and traumatic experiences on the development of psychosis (s. publication 4.2). Finally, our studies included only men; khat use is a predominantly male phenomenon, and psychotic experiences also differ between men and women, so findings might be explained by male characteristics. Future studies need to include gender as a factor to identify general mechanisms.

6. IMPORTANCE OF THE WORK AND FUTURE PLANS

A major focus of future research in psychiatric genetics should lie on the inclusion of populations currently heavily underrepresented in our studies. If we are truly committed to fighting mental illness and all its associated stigma, we will have to turn our back on our immediate surroundings and explore whether our approaches to research and therapy work not only in highly selected populations of industrialized countries but also in every corner of the world where many people suffer from a psychiatric disorder. Given the challenging conditions on site and little courage for investments, especially low-income countries have not yet had the chance to participate in global genetic collaborations. However, our initial feasibility studies (s. above) conducted in African countries are highly promising. Our early findings demonstrate the reliability and validity of biological research methods that are necessary for future genetics studies, deliver new insights into pathological pathways of mental disorders, underscore the need for further studying psychiatric illnesses, and call for adequate prevention and treatment tools.

The establishment of innovative scientific projects and of collaborations in the developing world are valuable not only for its theoretical use. Research programs have an enormous impact on both the socio-economic development as well as on the improvement of mental health care. They have a humanitarian aspect and fit the Sustainable Development Goals (SDG) of the United Nations. The research infrastructure currently implemented in Southwestern Ethiopia does not only benefit the further development of the Ethiopian psychiatric research infrastructure but it also positively impacts on the socioeconomic development and the improvement of mental health care in general. Service development, education, research, and publications are indispensable for strengthening the professional profile of psychiatry and for promoting mental health. Building capacity, supporting young scientists, sharing know-how, establishing new research methods, and making available the latest achievements in science and technology - all this has led to creating new workplaces (two more laboratory staff), to improving the reputation of local universities (high impact factor publication in World Psychiatry), to stopping “brain-drain”, and subsequently to improving the situation and the treatment options for patients on site after we had completed our study. Our biological research project with its special focus on cultural factors opened up new scientific insights and helped develop new resources in the country. Research also bears the potential to change attitudes and long-held beliefs. Through our engagement, our collaborators and we ourselves have been able to bring mental health and mental health research in Ethiopia into the limelight of public attention. Based on our findings, as well as our studies involving khat ad-

diction, various high-level talks between the Gilgel Gibe research group and the Federal Ministry of Health have been held since 2017 to discuss addiction rehabilitation and other projects. In cooperation with the Ethiopian Psychiatric Association and with the support of the African Association of Psychiatrists, the first regional WPA Congress was held in Addis Ababa in 2018. In this context, many creative African initiatives emerged, and the possibilities of international collaborations were discussed to improve mental health in Africa. In addition, we managed to present our work at the United Nations Office on Drugs and Crime (UNODC) in Vienna and developed a "UN Document" on "Treatment of Stimulant Use Disorders: Current Practices and Promising Perspectives". Finally in the presence of Bavarian Prime Minister Dr. Markus Söder, the Ethiopian Minister of State for Foreign Affairs, Dr. Markos Tekle, State Secretary Weigert and other representatives from politics, economy and science of Ethiopia and Germany, we signed a Memorandum of Understanding for the further cooperation between the IPPG (LMU), the Ethiopian Academy of Science and the College of Health Sciences of the University of Addis Ababa within the framework of a Bavarian-Ethiopian economic forum in April 2019.

Relevant publications in socio-economic context not presented here in detail:

Reta Y, Tesfaye M, Grimma E, Dehning S, **Adorjan K.** Public stigma against people with mental illness in Jimma Town, South West Ethiopia. *PLoS ONE.* 2016;11(11): e0163103. doi:10.1371/journal.pone.0163103.

Hadera E, Salelew E, Girma E, Dehning S, **Adorjan K**, Tesfaye M. Magnitude and Associated Factors of Perceived Stigma among Adults with Mental Illness in Ethiopia. *Psychiatry J.* 2019:8427561. doi: 10.1155/2019/842756.

Franke ML, Lersner, Essel OQ, **Adorjan K**, Schomerus G, Gómez-Carrillo A, Tam Ta TM, Böge K, Mobashery M, Dettling M, Diefenbacher, Angermeyer MC, Hahn E: The relationship between causal beliefs and desire for social distance towards people with schizophrenia and depression: Results from a survey of young Ghanaian adults. *Psychiatry Res.* 2019;(15)271:220-225.

Adorjan K, Mulugeta S, Odenwald M, Ndetei DM, Osman AH, Hautzinger M, Wolf S, Othman M, Kizilhan JI, Pogarell O, Schulze TG. Psychiatric care of refugees in Africa and the Middle East: Challenges and solutions. *Nervenarzt.* 2017;DOI 10.1007/s00115-017-0365-4.

Dehning, S, Jobst, A, **Adorjan, K.** Mental Health Masters support psychiatric health care in Ethiopia, *MMW Fortschr Med.* 2016;158:1.

Soboka M*, **Adorjan K***, Dehning S, Asaminew T, Abera M, Siebeck M, Tesfaye M, Jobst A. Evaluation of a Master of Science in Integrated Clinical and Community Mental Health (MSc ICCMH) program in Ethiopia. *Ger Med Sci.* 2018;18 (16):Doc04. doi: 10.3205/000266.

Future plans: Our projects can be seen as a set of pilot and feasibility studies to prepare a comprehensive population-based genetico-epidemiological study on various gene-environment interactions (khat, trauma, psychosis, risk and resilience) which should be carried out in the very near future. The infrastructure of GGFRC offers us a unique opportunity to build collectives of multiple-thousand people in a shortest period of time and to perform genetic studies in a way they have not yet been taken in Africa in this form and dimension so far. The extensive epidemiological registration of a population of 60,000 people, the stable population structure, and the quit stable environment, such as the urban and rural way of life with all its characteristics of an African country provide ideal conditions for this kind of proposition. The population is ideally suited to study the impact of polygenic risk profiles of various psychiatric disorders on behavioral traits and their interaction with environment.

In addition, we will endeavor our best efforts to facilitate the development of mutually beneficial collaboration in the following areas: 1) Promote collaborations between German and Ethiopian academic institutions and hospitals; 2) Support common scientific research, conferences, and workshops; 3) Foster exchange of information e.g. about national standards and legal practices (Ethics Committees); 4) Push development of an infrastructure for biological studies (laboratory medicine, genetics, biobank); 5) Promote education and teaching; 6) Build up improvement of mental health care (rehabilitation, innovations in the field of laboratory medicine, resulting in the distribution of new medicines e.g. lithium), and 7) Enhance collaborations with international organizations e.g. World Health Organisation (WHO), United Nations (UN), World Psychiatric Association (WPA) and local institutions (National Ethics Committee).

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