Algemene gegevens / General Information

Programma / Programme	:	**ERANID**
Subsidieronde / Subsidy round	:	**ERANID Second Joint Call**
Projecttitel / Project title	:	**Sensory Processing Sensitivity and drug Use recovery pathways**
Geplande startdatum / Planned start date	:	**01-05-2017**
Geplande duur / Planned duration	:	**36 maanden / months**
Datum indienen / Date of application	:	**11-10-2016**

Proposal submission file
ERANID Transnational Call 2016

Society and responses to drug use

SUBMISSION DEADLINE: - 18TH OCTOBER 2016 12.00 (CET)

Please refer to Guidelines for Applicants when filling out this form.

To be submitted by the Principal Investigator (PI) only and uploaded in the electronic submission system.

ERANID JOINT CALL SECRETARIAT (JCS):

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1. Summary and administrative information on applicants

1.1 General information on the project

Project Title	**Sensory Processing SensiTivity AND drug Use recovery Pathways**		
Acronym (max. 15 characters)	STANDUP		
Planned start date	1-05-2017	Total duration in months	36

	First and last name	Institution	Requested Funding (Euro)	Total cost(Euro)
PI	Judith Homberg	Radboud University Medical Centre	175.000	175.000
Co-PI 1	Fabio Fumagalli	University of Milan, Italy	100.000	150.000
Co-PI 2	Maria Melchior	Inserm	150.000	251.400
Co-PI 3	Boris R Quednow	University of Zurich, Switzerland	0	0
		Total	**425.000**	**576.400**

1.2 Keywords (max. 10, please use the same keywords as in the online submission system)

Individual differences; sensory processing sensitivity; social environment; illicit drug use; animal; causal; longitudinal cohort; biomarker; recovery

1.3 Please provide a plain language summary of the project (max. 10 lines)

Nowadays we are more and more exposed to external environmental stimuli and increased performance demands. This particularly affects those individuals who are more sensitive to such stimuli than average, like people high on the trait “sensory processing sensitivity (SPS). While these people generally have a benefit by being flexible and creative, they are also more susceptible to overstimulation. Drug use can serve as a dysfunctional way to deal with overstimulation. Our proposal will employ existing longitudinal human cohort studies and an environmentally-controlled animal study to delineate for the first time which social environmental factors increase drug use and which ones contribute to the recovery from drug use, in high SPS subjects. The identification of associated biomarkers will provide a mechanistic account for the ‘causing’ and ‘curing’ potential of social environmental factors in high SPS individuals.

1.4 Abstract (max. 1 page)

In digitalized postmodern life we are bombarded by stimuli, like socio-economic pressures (e.g. job instability and unemployment, fluctuations in financial resources), divorces, social media, multi-media, and many more. This particularly affects those individuals who are more sensitive to overwhelming stimuli than average, such as people with a high expression of the trait "sensory processing sensitivity (SPS; found in 20% of the human population). SPS is a concept derived from the observation that there are large individual differences in sensitivity or reactivity to the environment across > 100 animal species, which supports a strong biological foundation of SPS. People high on SPS are more sensitive to social environmental stimuli, both negative and positive ones. While these individuals are sensitive to overstimulation when exposed to too many or too intense adverse environmental stimuli, they are also highly flexible and creative when environmental conditions are calm or positive/supportive. Accordingly, in high SPS individuals (e.g. artists) negative external stimulation can induce drug use as a coping strategy, whereas supportive environmental stimuli can have the potential to reduce drug use despite adverse external stimulation. Indeed, cannabis and opioids help people to relax and to reduce stress, whereas stimulants enhance performance, possibly by increasing the amount of negative stimuli a person can deal with. **In our project "STANDUP" we aim to elucidate whether (1a) overstimulation increases drug use in individuals high on SPS and (1b) supportive social environmental factors can buffer against overstimulation and reduce drug use in individuals high on SPS. Additionally, we aim to identify (2) biomarkers of SPS-environment-drug use pathway links. By gaining insight into the social environmental factors that – as a function of SPS level – influence pathways to drug use and recovery, this project brings the opportunity to formulate recommendations for preventive and therapeutic interventions highlighting beneficial environmental factors.** To address aim (1a) and (1b) we will re-analyse existing longitudinal cohorts consisting of male and female long-term cannabis, opioid and stimulant (including new drugs like 2C-B, cathinon and ketamine) users, as well as healthy subjects. The cohorts contain data on life events (i.e. social environmental factors), psychopathology, social and personality assessments, drug use, demographics, and genetics, and we will include a questionnaire to assess SPS level. Furthermore, to study the relationship between SPS, social environmental factors and drug use pathways in a causal manner we develop a rat model for SPS which we subject to aversive and supportive social conditions and test for social and drug self-administration behaviour. Since the SPS concept is derived from animal studies, rats will have high translational value. To address aim (2) blood samples from the human cohorts, and blood and brains samples from the rats are used for biomarker assessments. **Our hypothesis is that individuals high on SPS have a hypersensitive brain due to reduced cortical inhibitory (GABAergic) control over excitatory (glutamatergic) neurons. High SPS individuals are expected to hit ceiling levels of neur(on)al activity, which shapes environmental sensitivity, flexibility and creativity, but leaves only a small dynamic range of neuroadaptation to deal with overstimulation/stress**. Therefore, our biomarker assessment will focus on markers of the GABAergic and glutamatergic systems. These biomarkers serve as guide for the assessment of the translational value of the animal study, and for the identification of beneficial environmental factors reducing drug use. That is, those environmentally-induced changes in drug use pathways paralleled by (changes in) biomarkers in humans and rats are likely most promising in the remediation of drug use. We use genetic data from human cohorts and existing rat data to further support the translation of data across species. The experimental design and the acceptability of the questionnaire to assess SPS levels will be discussed with a drug use expert, an SPS expert, and a health professional. These social actors will also provide advices on the formulation of a real-life intervention targeting specifically high SPS individuals. To sum up, our interdisciplinary research addresses a timely issue – overstimulation and social environmental factors – using a new psychological concept – SPS – that has the potential to gain unprecedented novel insights in factors that effectively reduce drug use and could be used in the design of interventions or the adjustment of existing ones.

1.5 General information on the consortium

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English: Department of Social Epidemiology, Pierre Louis Institute of Epidemiology and Public Health, INSERM U1136</td><td>Country</td><td colspan="2">France</td></tr>
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2. Description of the project

2.1 Description of the proposal, including aims, position in the state of the art, methodology and data to implement this methodology. Access to data must be explained and ensured (max.7 pages).

Substance use disorders are gene (G) x environment (E) disorders. Gene x environment interactions bring a rich source of individual differences in drug use and recovery pathways. According to the field of psychology, common genetic variants that are associated with psychiatric conditions are plasticity genes rather than vulnerability genes[2]. That is, because these genetic variants are so common in the human population that it is unlikely that they are maintained throughout evolution if they exert outright negative effects. Hence, these common genetic variants (which mostly involve monoaminergic genes) should bring the population as a whole a benefit for their maintenance. According to the *differential susceptibility* hypothesis for G x E interactions these plasticity genes confer environmental sensitivity, and thereby render individuals sensitive to both adverse and supportive environmental stimuli[2]. This concept, supported by an increasing number of studies, is of tremendous relevance for substance use disorders. Namely, these disorders have been associated with monoaminergic genes that function as plasticity genes[3]. The idea that these plasticity genes increase sensitivity to both adverse and supportive environmental stimuli[2] may well explain the inconsistencies among genetic association studies. That is, if only adverse stimuli are taken into account, the supportive stimuli may have hidden protective effects that are not considered, leading to variations in genetic association studies. Hence, it is essential to consider as many facets of environmental stimuli in G x E studies as possible.

Plasticity genes have been tentatively associated with the human trait of sensory processing sensitivity (SPS; found in 20% of the human population)[1;4;5]. In popular terms SPS is also called the High Sensitivity Personality (HSP) trait[1]. This trait is derived from the observation that in more than 100 animal species there are large individual differences in sensitivity or reactivity to the environment[1], implying that it has a strong biological foundation. In humans it shapes environmental sensitivity (i.e. sensitivity to both adverse and supportive environmental factors) and is associated with creativity and flexibility. Scientifically, individuals at the 'high SPS' extreme of the whole spectrum of sensitivity levels are characterized by: 1. Stronger emotional reactivity. 2. Deeper processing of sensory information. 3. Greater awareness of subtle environmental stimuli. 4. Enhanced susceptibility to overstimulation[57]. Based on facets 1, 2 and 3, high SPS individuals are highly conscientious, creative, have a rich "inner life" and a very well developed intuition, and excel in empathy. That is, the sensory information they perceive is 'enriched' by previous (emotional) experiences which influence their perception and allow them to respond adaptively to (social) environmental stimuli. Artists often are high on SPS. A down-side of being sensitive to environmental stimuli is increased susceptibility to overstimulation when (adverse) environmental stimuli are too overwhelming (facet 4). This can lead to stress and social withdrawal[1]. In postmodern life we are bombarded by environmental stimuli, like socio-economic pressures, divorces, social media, and many more. This puts high demands on people high on SPS. Drug use can serve as a dysfunctional means to reduce external stimulation, which may go awry in some and lead to compulsive drug use and thereby a substance use disorder. For instance, opioids allow a person to relax and to reduce socio-emotional stress[48,49]. Likewise, cannabis is commonly used to cope with stress, particularly by individuals with life stress experiences[6]. Furthermore, environmental adversity increases and environmental enrichment decreases the choice for cocaine[43,44,45], cannabis[7] and other psychoactive drugs. Therefore it has been postulated that they are consumed for their effects on mental states as a functional adaptation to modern environments[46]. Stimulants may also be used to deal with overstimulation, possibly by increasing the threshold beyond which individuals feel overstimulated. In support of a link between stimulant use and SPS, we have shown that there is a strong association between stimulant use and anxiety[8] (SPS facet 1), and that awareness of subtle environmental stimuli is increased in stimulant users[47] (SPS facet 3). As the environmental stimuli we are exposed to keep on rising, the need to cope with overstimulation continues to rises as well. On a more positive note, individuals high on SPS who have developed psychopathology remain sensitive to supportive (social) environmental stimuli[10], which can offer a foothold for the design of individualized interventions. **Consequently, in our**

***ERANID* project "STANDUP" we aim to elucidate whether (1a) overstimulation increases drug use in individuals high on SPS individuals and (1b) supportive social environmental factors can buffer against overstimulation and reduce drug use in individuals high on SPS. Additionally, we aim to identify (2) biomarkers of SPS-environment-drug use pathway links. By gaining insight into the social environmental factors that – as a function of SPS level – influence pathways to drug use and recovery, this project brings the opportunity to formulate recommendations for propitious therapeutic interventions relying on supportive social environmental factors.**

Psychologists propose that high SPS is related to a hypersensitive brain[10]. However, for neuroscientists and neuropsychiatrists it is unclear what this precisely means and how it could contribute to drug use and recovery. Animal studies can help to clarify how the high SPS brain is wired.

SPS is likely founded by an array of plasticity genes[11], and one of them involves the low activity short (s) allelic variant of the common serotonin transporter (5-HTT) linked polymorphic region (5-HTTLPR s-allele)[5]. In support, there are strong phenotypic similarities between the 5-HTTLPR s-allele in humans/5-HTT knockout in rodents and SPS[57]. Briefly, the four SPS facets and corresponding rat phenotypes [BOX 1] are found in 5-HTTLPR s-allele carriers and 5-HTT knockout rodents. As an example, Dr. Homberg found that 5-HTT knockout (5-HTT$^{-/-}$) rats display 1. increased anxiety when exposed to novel environments, like the elevated plus maze[12], 2. prolonged freezing in response to a threat predicting cue, serving to scan the environment[57] and deep processing of sensory information[13;14], 3. increased prepulse inhibition[15], reflecting sensitivity to environmental subtleties, and 4. susceptibility to overstimulation, leading to social avoidance[16]. These 5-HTT$^{-/-}$ rats also display increased self-administration of cocaine[17;18], MDMA[19], and amphetamine (Verheij et al. unpublished data). During withdrawal from cocaine self-administration 5-HTT$^{-/-}$, compared to wild-type, rats show a negative emotional state (Verheij et al. submitted), which may be the outcome of over-stimulation and motivate the animals to use drugs as self-medication. Like 5-HTT$^{-/-}$ rats, 5-HTTLPR s-allele carriers show increased vulnerability to substance use disorders[20;21] and increased anxiety[22], indicating that the 5-HTT$^{-/-}$ rat findings have high translational value. Thereby, these animals can provide mechanistic hints about neural mechanisms underlying SPS. First, amygdala excitatory neurons displayed significantly higher spine density in naïve 5-HTT$^{-/-}$ compared to wild-type mice[23], which is thought to represent a structural correlate for excitatory synaptic contact and may be triggered by the release of inhibitory control[57]. A high spine density in the amygdala of 5-HTT$^{-/-}$ rodents may represent traces of enhanced emotional reactivity (SPS facet 1; BOX 1). Importantly, repeated social stress-experiences led to increased dendritic spine density in the amygdala of wild-type but not 5-HTT$^{-/-}$ animals. A similar observation was obtained for the prefrontal cortex[24], which is implicated in sensory information processing (SPS facet 2; BOX 1). This ceiling effect may well contribute to susceptibility to overstimulation (SPS facet 4, BOX 1). Furthermore, we found hyperexcitability in the somatosensory cortex of the 5-HTT$^{-/-}$ rats (Miceli et al. under revision). This was associated with a reduced GABAA α1 subunit expression[25], reduced ratio of GABA versus AMPA (glutamate) currents onto excitatory neurons, and a decreased number of inhibitory contacts on excitatory neurons in the knockout rats (Miceli et al. under revision). This hyperexcitability due to reduced inhibitory control in a cortical network that functions as a gate for incoming sensory information, likely contributes to greater awareness of environmental subtleties (SPS facet 3; BOX 1). Finally, there is evidence that pharmacological interventions reducing cocaine self-administration or reinstatement increase GABA levels[26;27;28]. **In sum, we postulate that high SPS individuals quickly hit ceiling levels of neural activity, which leaves only a small dynamic range for neuroadaptations to deal with overstimulation, but simultaneously increases sensitivity to supportive environmental stimuli leading to reduced drug use and increased recovery.**

BOX 1: High SPS is characterized by[1]:	**Corresponding rat phenotypes**
① Stronger emotional reactivity	① Increased anxiety
② Deeper processing of sensory information	② Prolonged freezing to a threat predicting cue
③ Greater awareness of subtle stimuli	③ Increased prepulse inhibition
④ Enhanced susceptibility to overstimulation	④ Social withdrawal

This hypothesis is important to define biomarkers of drug use and recovery in relation to SPS. Besides the mPFC and amygdala, the nucleus accumbens (responsible for translation of motivation into action and centrally implicated in substance use disorders) and insula (signaling awareness of interoceptive signals and thereby the urge to take drugs[29], and centrally implicated in SPS[30]) may also be subject to reduced inhibitory (GABAergic) control over excitatory (glutamatergic; GLU) neurons. Of interest, both GABA and GLU are synthesized from glutamine (GLN) in astrocytes[31]. This has led to the concept of the GLU–GLN-GABA cycle, which predicts that GLU leaving the neuronal compartment is reuptaken to the astrocytic compartment via glutamate transporters, where GLU is metabolized, at least partly, to GLN, via a highly active GLN synthase (GS) pathway. GLN released by astrocytes can also function as precursor for the inhibitory neurotransmitter GABA, through GAD[32]. Animal experiments have demonstrated that a single dose of psychostimulants (30 mg/kg) leads to the down-regulation of the GLN/GLU and altered GABA/GLU ratios[33]. Furthermore, Dr. Fumagalli found that acute stress reduced the GABA/GLU balance in the prefrontal cortex of rats chronically exposed to cocaine[35], a biological state that may be pre-existing in individuals high on SPS. Furthermore, using magnetic resonance spectroscopy (MRS) in subjects addicted to methamphetamine, abnormal GLU-GLN circulation in neuroglia cells was found[34]. Moreover, Prof.Dr. Quednow recently showed using MRS that higher weekly cocaine use and higher cocaine hair concentrations were associated with lower GLN/creatine ratios in the pregenual anterior cingulate cortex of chronic cocaine users[35]. Based on these data, we suggest that a potential imbalance of the GLN-GLU-GABA cycle in high SPS individuals increases their susceptibility to drug use in case of overstimulations as well as their probability to recover from drug use when exposed to supportive social environmental stimuli.

To achieve our aims and test our hypothesis we have formulated the following **Key Objectives** and corresponding **Workpackages (WPs):**

1. **To assess the impact of adverse and supportive social environmental stimuli on drug use recovery trajectories in humans and rats as a function of SPS (WP1)**
2. **To identity the biomarkers contributing to variations in drug use and recovery as a function of (social) environmental stimuli and SPS (WP2)**

Hence, we will combine preclinical and clinical research to elucidate which social environmental factors have the potency to increase and reduce drug use in individuals high on SPS. We include gender as a potential factor in our study as SPS is equally found in males and females[1], while substance use disorders are generally more prevalent in men compared to women. Possibly, gender differences in coping with stress, which are partly shaped by prevailing cultural norms regarding traditional gender roles, and can be induced by overstimulation ('fight and flight' in males and 'tend and befriend' in females[36]) steer the male preponderance in substance use disorders. Since cultural factors do not play a role in rats, our cross-species approach will reveal whether gender-related biological and/or cultural factors are implicated in the SPS-drug use-recovery link. As a follow-up, this could provide a basis for the formulation of recommendations for the design of interventions containing supportive elements (e.g. strengthening emotional resilience and a positive social environment) tailored to reduce drug use in individuals high on SPS. We have contact with stakeholder Dr. Michael Pluess (Queen Mary University of London, UK) - who successfully developed an intervention to reduce depression scores in high SPS children living in deprived neighborhoods[10] – to advice us on the use of the questionnaire to assess SPS levels in humans and assess our findings and consider their usability in the formulation of an intervention tailored to reduce drug use. Furthermore, Mr. Marcello Van Den Anker (drug use expert helping drug users to recover; http://www.bureau-marcello.nl/) and the French Fédération Addiction (http://www.federationaddiction.fr/) will provide us input on the precise research questions we will address in the human cohort studies. The French Fédération Addiction will also validate for us the acceptability of the questionnaire used to assess SPS levels among a sample of patients and professionals, will help us to spread the results we collect to the community of health professionals, and will give, together with Dr. Pluess and Mr. Van Den Anker advices for the to design or adapt real-life interventions.

Regarding Key Objective 1 we make use of existing longitudinal human databases. We will collaborate with Prof.Dr. B. Boris Quednow from Switzerland who has built up a longitudinal cohort of 190 individuals (115 males, 75 females) with chronic psychostimulant (primarily

cocaine or MDMA, secondary 2C-B, cathinon and ketamine) users and 105 matched healthy controls (Zurich Cocaine Cognition Study, ZuCo^{2}St). The cohort is well characterized in terms of demographics, social life events, sensorimotor gating (PPI)[37], neuropsychology including social cognition and interaction[38-40], behavioural inhibition[40;41], psychopathology, personality questionnaires, quantitative 6-month hair analyses, and genetics[9;42]. Additionally, for a smaller subpopulation of the ZuCo^{2}St [11C]ABP-688 positron emission tomography (PET) scans measuring metabotropic glutamate 5 (mGluR5) receptors and MRS scans measuring GABA, GLU and GLN are available (18 cocaine users, 18 controls)[35;43]. Moreover, for 81 cocaine users and 51 controls a one-year follow-up assessment exists. Finally, blood-derived RNA is available and will be used for Key Objective 2. However, information regarding SPS is not available yet. Therefore, we will ask all participants to complete the HSP (Highly Sensitive Person) questionnaire in order to assess the level of SPS. This enables us to correlate SPS with social cognitive markers, GABA, GLU and GLN concentrations in the prefrontal cortex, and to predict from SPS scores if users have increased or decreased their drug use in the follow-up (as objectively measured by hair analyses). Furthermore, Dr. Quednow has started (based on own funding) a new studies on social stress in 40 prescription-opioid users and 40 healthy subjects (~50:50 male:female), in which the HSP questionnaire has already been implemented. For this cohort Dr. Quednow collected cognitive data (specifically social cognition and interaction) and determined stress hormones (baseline and after a social exclusion task). Moreover, he will start a study with 100 cannabis users and 100 drug-naïve controls (~60:40 male:female) in Summer 2017, in which with the HSP questionnaire will be implemented as well. In this study participants will be subjected to a broad neuropsychological characterisation as well as comprehensive neuroimaging studies. Here, associations between amygdala, PFC and SPS can be investigated in multiple ways.

Second, we will test whether SPS and characteristics of the social environment predict patterns of cannabis use over time – and particularly recovery from heavy use, using data from the TEMPO cohort study in France (www.tempo.inserm.fr, Principal Investigator Maria Melchior). The TEMPO study, started in 2009, among 1103 individuals aged 22 to 35 years (average age 29 years), who had previously participated in a study on children's mental health difficulties and access to treatment in 1991[44]. Participants had also been assessed in 1999 – with a focus on addictive behaviors including cannabis use; since the TEMPO cohort was set up, participants were followed in 2011 (by phone interview) and 2015 (by self-reported questionnaire), to follow changes in socio-demographic circumstances (education, employment, family life) as well as addictive behaviors including cannabis and mental health. In 2015, participants provided saliva samples (n=533) from which DNA on 96 single nucleotide polymorphisms potentially related to addictive behaviors was extracted. TEMPO participants are spread out throughout and all have a parent who takes part in the longitudinal GAZEL cohort study set up in 1989 (www.gazel.inserm.fr), which makes it possible to link youths' behavior to their parents' characteristics. Moreover, the TEMPO study follows a cohort of youths from childhood into young adulthood, that is during the period when cannabis use onsets and can also decrease as individuals move from adolescent to adult social roles. SPS was not directly ascertained in this study, but the HSP (Highly Sensitive Person) questionnaire can be added to the next wave of data collection in 2017. This wave of data collection will also make it possible to ascertain current use of cannabis as well as experience with new psychoactive substances. Moreover, several proxies of SPS are already available, such as high emotionality (including symptoms of anxiety) in childhood, adolescence and young adulthood (as measured by the Child Behavioral Checklist - CBCL[45,46], clinically relevant anxiety as ascertained by the DSM4-based MINI questionnaire, the Emotionality, Activity and Sociability – EAS scale, and the Ten Item Personality Inventory – TIPI[47]). These diverse and repeated measures of anxiety can be aggregated in order to identify individuals who are most reactive to their environment. Additionally, participants' experience of life events was ascertained in 1991, 2009 and 2011 as well as their reactions to those life events, which can also serve as a proxy measure of SPS. Finally, we are also in the position to use variations in the 5-HTTLPR gene (s vs. l-allele carriers) to identify participants with a biological predisposition to SPS. In terms of social environmental characteristics, the TEMPO study collected rich and repeated information on participants' socio-demographic position, financial difficulties, family status, social supports, as well as life events (e.g. unemployment, marital separation). Cannabis use – the most frequent illegal drug in the general population - was ascertained by the frequency of use in 1999, 2009, 2011 and 2015, as well as clinically-relevant abuse, as identified by the Cannabis Abuse

Screening Test – CAST[48] in 2009, 2011 and 2015. The use of other substance (tobacco, alcohol, psychoactive drugs, and illegal drugs other than cannabis) and mental health difficulties (internalizing and externalizing symptoms, DSM-4 diagnosis of major depression, Attention Deficit Hyperactivity Disorder) were ascertained in 2011 using the MINI standardized instrument[49]. 60% of the TEMPO cohort study is female, allowing us to test gender differences in the relationship between SPS, the social environment, and recovery from high cannabis use.

While all this information is highly valuable, human studies are of observational nature, and causal assessments are complex to establish. We overcome these limitations by the use of parallel rodent studies. We will link available 5-HTT knockout rat data on drug self-administration and SPS-related phenotypes for a cross-species comparison with 5-HTTLPR genotype data in human cohorts, to support the translational value of rat-derived data. Furthermore, we will develop here a novel rat model for SPS based on the 5-HTT knockout rat findings, aligned to the first three of the four SPS facets as presented in BOX 1. This new rat model making use of natural variance in environmental sensitivity among animals will be established by Dr. Homberg and is expected to approach the multi-genetic nature of SPS. Using this SPS rat model we will experimentally collect the same measures, but with the advantage of rats' short life span and controlling environmental factors (i.e. adverse and supportive social environmental factors alone and combined) to study the causal relationship between SPS-social environmental factors and drug use. Furthermore, animal studies allow the investigation of behavioural, blood and brain biomarkers before, during and after drug use, as well as the link between brain to blood biomarkers. The measurement of common blood and brain biomarkers in human subjects and the animals, as will be done in Key Objective 2, serves two purposes: 1. it assists the identification of supportive social environmental factors facilitating recovery from drug use, and 2. it further ensures the translational value of rat-derived data. Dr. Fumagalli will assess biomarkers in blood-derived RNA samples of drug users and in blood and brain RNA samples of rats at different stages of the drug use pathway as a function of social environmental stimuli.

In sum, using interdisciplinary and translational approaches, we will assess the relationship between SPS, social environmental factors and drug use pathways. For this purpose, we will integrate complementary expertise in the fields of neuropsychiatry, psychology, epidemiology, neurosciences and molecular neurobiology. The project will benefit from the collaborative efforts of preclinical researchers and, epidemiologists and psychologists with outstanding experience in their respective fields.

Reference List (for entire proposal; bold references are from applicants/stakeholders)

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2.2 Description of how the proposal addresses the requirements of the call (max. 1 page).

Our project looks into the multifaceted links between social environmental factors, drug use and recovery. We focus on critical social environmental factors such as employment and unemployment. These links will be studied as a function of SPS, a biologically grounded characteristic underlying individual differences in environmental sensitivity. We consider coping with overstimulation in individuals who are more sensitive than average to environmental stimuli as a motive for drug use. We study which type(s) of supportive social environmental stimuli (e.g. return to employment, a new romantic relationship, an increase in social support) help to reduce drug use in high SPS overstimulated individuals. Therefore, socio-epidemiological studies will be implemented to assess the influence of socio-economic factors, life events and transitions in social behaviour with regard to trajectories of drug use and pathways to recovery, in individuals high on SPS. We will provide an exhaustive characterization of the mechanisms linking SPS, drug use and recovery, by looking at different dimensions of SPS such as stronger emotional reactivity, deeper processing of sensory information and greater awareness of subtle environmental stimuli. In line with the requirements of the call, we implement advices of Dr. Pluess (child psychologist, SPS expert), Mr. Marcello Van den Anker (drug use expert helping drug users to recover), and Mrs. Laurène Collard of the French Fédération Addiction in the study design. The collaboration with the French Fédération Addiction will also make it possible to test the HSP questionnaire among a sample of patients (n=100) and discuss it with professionals intervening with persons using drugs to verify its acceptability and usefulness in clinical practice. We will make use of existing ethically approved (see section 6.3) longitudinal cohorts of male and female drug users and non-drug users in France and Switzerland. This transnational approach allows the identification of common traits as well as sex-specific social environmental factors that play a key role in drug use and recovery. We focus on cannabis with stress-reducing capacities which is shared by the existing cohorts from France and Switzerland. We also have access to a cohort of opioid users in Switzerland. Furthermore, we include performance enhancing stimulant drugs (cocaine, MDMA, and new synthetic drugs like 2C-B and cathinon), such that we are able to investigate whether the link between SPS, social environmental factors, and the pathways to drug use and recovery are dependent on the type of drug. Since the use of new drugs like 2C-B, cathinon and ketamine in Europe is limited and it is imperative to make use of existing cohorts, we consider stimulant use as predictive for use and recovery pathways for such new drugs. Additionally, we use existing data on self-administration in serotonin transporter knockout rats showing SPS-related phenotypes to validate – in combination with genetics data derived from the human cohorts - the translational value of rat-derived behavioural data. Furthermore, we establish a new rat model for SPS modeling the mult-genetic nature of SPS and use male and female rats to assess the causal relationship between SPS, type of social environmental factors and the dynamics of drug use. The human and animal studies are further linked by comparing changes in biomarkers as function of SPS and social environmental factors. This serves to support the translational value of the rat findings and to evaluate the efficacy of environmental factors influencing drug use and recovery. This evaluation will be driven by multivariate analyses across factors influencing drug use increases and decreases. The data will be published in peer-reviewed international open access journals for widespread dissemination of findings. Furthermore, a qualitative open access review will provide the most comprehensive account of SPS-social environment-drug use-recovery relationships, which will be complemented by data on underlying behavioural and molecular mechanisms. In France, the results of the project will be disseminated to health professionals addressing the needs of persons using drugs through a short published brochure produced at the end of the project, web-based information, and meetings with groups of health professionals. Based on advices from the French Fédération Addiction, Mr. Van den Anker and Dr. Pluess we will propose a real-life intervention. Thus, based on all these considerations, our project perfectly fits with the requirements of the call. By integrating different disciplines (neuropsychiatry, psychology, epidemiology, neuroscience, molecular neurobiology) it represents an unprecedented opportunity to get insights into questions related to pathways to illicit drug use and recovery in our modern society. We will deliver important data on the ways in which the social environment influences the use of cannabis, opioids, psychostimulants, as well as new drugs like 2C-B, ketamine and cathinon, in individuals high on SPS.

2.3 Description of ongoing projects related to the present topic indicating funding sources and possible overlaps with proposal (max. 1 page).

Judith Homberg (NL): Dr. Homberg, who finished her PhD on individual differences in addictive behaviour in 2004, is currently using serotonin transporter knockout rats to unravel how trait anxiety increases compulsive drug self-administration. More specifically, in collaboration with Prof.Dr. George Koob (now: head of NIAAA in the USA) she studies the synergism between the 'emotional' serotonin system and the corticotrophin releasing factor (CRF) 'stress' system in susceptibility to compulsive cocaine self-administration. The data reveal that the CRF stress system is upregulated in the serotonin transporter knockout rats that show increased trait anxiety and compulsive cocaine self-administration. These findings are relevant for the present project, because it demonstrates that knockout rats – which display SPS-like phenotypes – engage into compulsive cocaine self-administration. In a second project it is investigated whether serotonin transporter gene variance increases compulsive cocaine self-administration behaviour due to increased environmental sensitivity, using tools like D-cycloserine (a glutamate NMDA receptor partial agonist) and counterconditioning. Since we make use of a novel rat model for SPS in this project and will attain a prospective experimental design that includes positive and negative environmental challenges the current project complements the ongoing studies.

Fabio Fumagalli (IT): Dr. Fumagalli, who finished his Ph.D. in 1996, recently investigated the effects of developmental exposure to cocaine on brain plasticity, focusing on the glutamate system, the GABA system and the neurotrophin BDNF. Dr. Fumagalli also investigates how stress affects the molecular response to cocaine in the brain of adolescent rats. His recent data reveal that, in cocaine-treated animals, stress dynamically altered the glutamatergic synapse. Notably, the hyperactivation of the glutamate system was observed concomitantly with a reduction of crucial determinants of the GABA system: this topic is pivotal with respect to this proposal showing that Dr. Fumagalli's expertise fits perfectly with the aims of the proposal.

Maria Melchior (FR): Dr. Melchior, who finished her PhD on social inequalities with regard to mortality in 2004, is a social epidemiologist specializing in the study of the role of the social environment with regard to life course trajectories of substance use and mental health. In the TEMPO study, she has shown the role of socioeconomic position – and particularly unemployment – as a key determinant of tobacco and cannabis smoking in young adulthood among a contemporary sample of young people in France. Her research also emphasizes the role of social isolation and lack of social support with regard to emotional difficulties such as symptoms of depression and anxiety as well as psychoactive substance use.

Boris B. Quednow (CH): The ZuCo^{2}St was funded by the Swiss National Science Foundation (SNSF) in the frame of a SNSF-professorship position for Boris B. Quednow (PP00P1-123516/1 and PP00P1-146326/1). The ZuCo^{2}St provides the best characterized population of cocaine users worldwide available so far (see above). Since his PhD Dr. Quednow has investigated the predispositions and consequences of illegal drug use (e.g., MDMA, cocaine, methylphenidate, cannabis, prescription opioids) with regard to cognition and personality. Moreover, he is highly interested in drug x gene interactions on information processing and cognition in human drug using populations. Recently, he has shown that many cognitive disturbances are reversible if cocaine abstinence is established but only in late-onset users. Moreover, he has shown that the serotonin transporter polymorphism modulates the risk for working memory deficits in cocaine users, while noradrenergic polymorphisms moderate delay discounting problems in the same sample. Finally, he has investigated the role of glutamate in cocaine addiction with molecular imaging techniques such as PET and MRS.

2.4 Describe the innovative approach and the added value of the proposed solutions compared to existing ones and makes a risk assessment (max. 2 pages).

Our hypothesis is that individuals high on SPS are on the one hand sensitive to overstimulation and use drugs as a coping strategy and on the other hand they are sensitive to supportive social environmental factors that can aid recovery. This is a highly timely topic, since we are in current life more and more bombarded with environmental stimuli due to socio-economic pressures and modern technologies, but live in societies that have built-in supportive social environmental factors as well.

Drug use represents an area of substantial interest for the scientific community. While the influence of the social environment has been previously pointed out, it is gaining further attention, mostly now that the SPS trait is becoming accepted as a key factor determining individual differences in environmental sensitivity. Specifically important is that SPS is derived from the observation of individual differences in environmental sensitivity/reactivity in > 100 animals species, and therefore likely has a strong biological foundation. This implies that SPS has heuristic value to advance our understanding of individual differences in drug use trajectories and recovery in combination with social environmental factors which we are exposed to in current society. We will also examine gender in close detail, since males and females may be differentially sensitive to social environmental factors that can trigger overstimulation and that can aid in the recovery from drug use. We combine human and rat studies. The human studies provide the advantage of longitudinally and transnationally testing associations between SPS and social environment characteristics in large cohorts of individuals using 'stress-reducing' or 'performance-enhancing' drugs. These data sources offer access to a wealth of data on individuals' psychological characteristics (including SPS proxies), demographics, socio-economic factors, genetics, and brain imaging that will serve to understand the SPS-environment-drug use-recovery link. Hence, there are no risks related to patient recruitment and statistical power. Of interest, serotonin transporter gene variance has been linked to SPS in humans and animals, and we have data on serotonin transporter linked polymorphic region (5-HTTLPR) genotype in the human cohorts as well as data on drug self-administration in serotonin transporter knockout rats. A 'serotonin transporter' cross-species comparison allows an initial assessment of the SPS-drug use link. Additionally, using a novel rat model for 'multi-genetic' SPS we will causally investigate whether supportive environmental factors can buffer against the negative effects of overstimulation and reduce drug intake. The rats also offer the possibility to collect brains for biomarker studies, which is not possible in humans. We ensure the translational value of the rat findings by the cross-species transporter data comparison and by studying the same biomarkers in humans (blood) and rats (blood and brain). The human and rat studies together provide an outlook for who benefits from what type of social environmental factors in the pathway to recovery from drug use, which cannot be determined in human studies alone because of their observational nature and the impossibility to asses changes in brain biomarkers as function of social environmental factors. Hence, we join the strengths of human and animal research.

To the best of our knowledge, this represents the first attempt to provide important new information relative to the relationship between SPS and drug use trajectories and recovery and to decipher the underlying mechanisms. As set out in section 2.1., there are multiple indices for this relationship, further supported by our published and preliminary data (see section 3). Nonetheless, the direct association between SPS and drug use and recovery remains to be established, rendering this project a high risk-high gain one. Indeed, if this project is successful, the results will ultimately help to define strategies that make use of supportive environmental stimuli to promote resilience to overstimulation and that may reduce drug use in high SPS subjects. These will be distinctive from existing strategies aiming to reduce automatic responses to drug-related cues (e.g. cognitive bias modification[50]) or to reinforce abstinence by monetary rewards[51]. By focusing on frequent socio-economic factors (e.g. unemployment, financial difficulties), our project will have important influences on strategies aiming to reduce drug use and stimulate recovery. By identifying ways in which our research findings can be translated into practice, we will be in the position to deliver results that are highly relevant to pracitionners and policy makers.

2.5 Describe the added value of the proposed international collaboration: please explain the inter- or transnational dimension of the topic of your proposal and the chosen multidisciplinary approach to address it (max. 1 page).

This *ERANID* consortium gathers 4 partners with unique and highly complementary expertise:

Dr. Homberg is a neuroscientist with expertise in individual differences in vulnerability to addictive behaviour. She contributes to this project by using a novel rat model for SPS and testing the animals for drug use as function of social environmental conditions. She collects brain and blood samples for biomarker assessments by Dr. Fumagalli.

Dr. Fumagalli is a molecular biologist with expertise in investigating the molecular determinants of the effects of drugs in the brain. He contributes to the project by examining the glutamate/GABA balance in human and animal samples via molecular approaches in search for biomarkers of SPS.

Dr. Maria Melchior is a social epidemiologist specialized in the study of social determinants of trajectories of substance use and mental health, with a particular interest in transitions between adolescence and young adulthood. She contributes to the project through her expertise on characteristics of the social environment that influence drug use at a population level and that may be particularly amenable to change through specially-designed interventions.

Boris B. Quednow is a clinical neuropsychologist with expertise in substance use disorders (and schizophrenia), cognition (including social cognition and interaction), sensorimotor gating, molecular imaging, and psychiatric genetics. He contributes by making the data of the ZuCo^{2}St opioid, and cannabis cohorts available for this project.

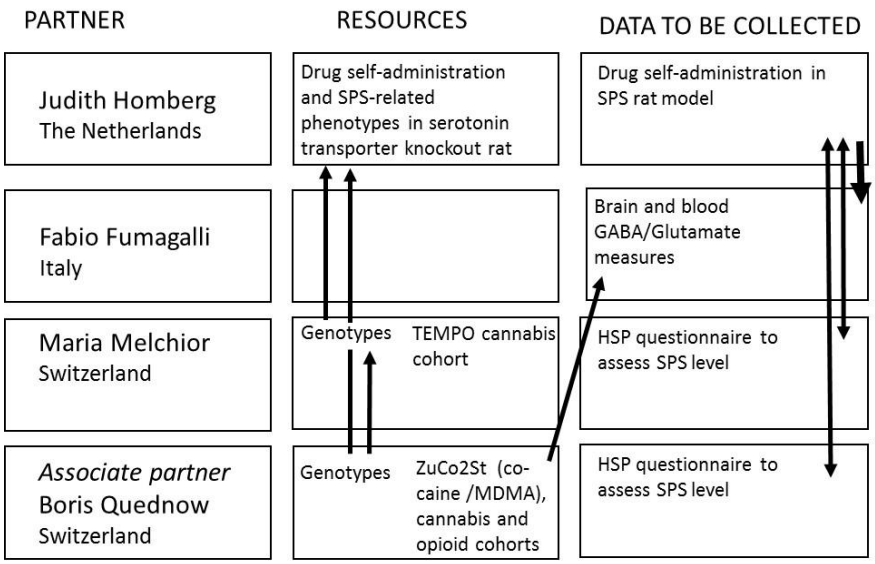

Figure 5: Overview on the work flow of STANDUP and the added value gained by the interaction of the partners

Two partners already interact, which strengthens the commitment to this consortium. Judith Homberg and Fabio Fumagalli have long-standing interaction, initially through their direct colleagues and now in a direct collaboration on a study examining the role of BDNF in compulsive cocaine self-administration in rats (Verheij, et al., 2016). In this collaboration, the Homberg lab has performed the behavioural experiments and collected animal brains, which were shipped to Milan for protein analyses. Quednow and Homberg met during the AGNP meeting in München in September 2015, when presenting data on cocaine addiction in the same session. As of now, there are no existing collaborations between Homberg, Fumagalli, Melchior and Quednow. Hence, the consortium itself is novel, which provides the opportunity to leverage translational data on a novel concept (sensory processing sensitivity; SPS) that neither of the partners could do alone. We see this as a singular project and not as separate projects that will be stitched together at the end. This integrated approach requires combined efforts and coordination, which we are planning through joint meetings of the PIs and key trainees and an open line of communication of data (see section 7).

3. Description of the project plan

With respect to the objectives of the project and the chosen methodology and data to implement it (see item 2.1), please describe the tasks involved in each work package along a time plan (including a Grant chart providing a schedule for the completion of work, indicating the timing of key milestones). For each task and work package, the project coordination and management as well as the division of labour will be provided (effort estimated in Person/Month per project partner) (max.5 pages).

Overview:

WP nr.	WP title	Start	End
1	**To assess the impact of adverse and supportive stimuli on pathways to drug use and recovery in humans and rats as a function of SPS**	1	36
2	**To identity the biomarkers contributing to variation in drug use pathways as function of (social) environmental stimuli and level of SPS**	13	36
3	**Dissemination: scientific & public engagement**	25	After end of project

Dissemination activities are descripted in section 6.2

WP1: Task 1.1. Humans [QUEDNOW**]**

Illicit drug users: We will re-assess all participants (2/3 men and 1/3 women) from the existing longitudinal ZuCo^{2}St cohort with the HSP questionnaire in order to assess SPS. This is the 27-item questionnaire: http://hsperson.com/pdf/HSPSCALE_2007_research.pdf. If not possible, a SPS proxy scale can be extracted from several questionnaires used in the ZuCo^{2}St cohort such as the Temperament Character Inventory, Barratt Impulsiveness Scale, Beck Depression Inventory, Attention Deficit/Hyperactivity Disorder Self-Report Scale, SCID-II questionnaire, and Machiavelli Questionnaire. These questionnaires provide an item pool of >500 items. Due to the highly redundant nature of personality and psychopathology questionnaires a large overlap exists between the used scales and the HSP scale. This overlap can be identified and an SPS proxy scale can be calculated. The ZuCo^{2}St cohort also contains abundant information on the use of new stimulant drugs (2C-B, ketamine, cathinone), and on social environmental factors, including income, type of school, social network size etc. Furthermore, Dr. Quednow has started a new longitudinal study on social stress in prescription-opioid users (~50:50 male:female), in which the HSP questionnaire has been implemented already. Dr. Finally, Dr. Quednow will start a cannabis cohort (~60:40 male:female) study containing demographic, social environmental, personality, cognitive, and structural and functional imaging data. The following questions can be potentially answered:

1. Do recreational/dependent stimulant and opioid users differ from controls regarding SPS?
2. Which drug profile found in hair samples is predictive for SPS (or vice versa)?
3. Are high/low SPS individuals vulnerable to an increase or decrease in their drug consumption during the follow-up interval due to social environmental changes and is this gender-dependent?
4. Do polymorphisms in monoamine system genes (e.g. 5-HTTLPR) modulate SPS in drug users and controls as in 5-HTT knockout rats?
5. Is SPS correlated with increased emotional reactivity (a proxy of SPS facet 1) in drug users and controls as animal studies suggest?
6. Is SPS correlated with increased behavioural inhibition to scan the environment (a proxy of SPS facet 2) in drug users and controls as animal studies suggest?
7. Is SPS correlated with sensorimotor gating (PPI; a proxy of SPS facet 3) in human drug users and controls as animal studies suggest?
8. Is SPS correlated with social cognition and interaction changes (a proxy of SPS facet 4) in drug users and controls?
9. Is SPS correlated with cerebral glutamate markers such as cortical/subcortical mGluR5 density (measured with [11C]ABP-688 PET) or GLU/GLN concentrations in the prefrontal cortex (measured with MRS) in drug users and/or controls?

WP1: Task 1.2. Humans [MELCHIOR**]**
All TEMPO study participants will be asked to complete the 27-item HSP questionnaire in order to assess SPS http://hsperson.com/pdf/HSPSCALE_2007_research.pdf. Before these data are available, an SPS proxy will be extracted from the several already-existing sources of information on symptoms of anxiety (repeated CBCL measures, MINI), personality (EAS, TIPI), reactions to life events as well as 5-HTTLPR genotype. Latent class analyses will serve to establish a profile of participants particularly sensitive to their environment. In terms of social environmental challenges, analyses will focus on the role of unemployment, financial difficulties and marital separation as key life circumstances that may influence drug use. Regarding positive aspects of the social environment which may be related to drug use recovery, we will specifically focus on social networks and support which were measured on several occasions using the Berkman Social Networks and support inventory[52], as well as labour market entry (for participants who just completed their education) or return (for participants who experienced a period of unemployment). TEMPO study participants reported on the frequency of cannabis use on 4 occasions (1999, 2009, 2011, 2015) and cannabis abuse was ascertained on three occasions (2009, 2011, 2015). This will enable us to establish trajectories of cannabis use using group-based trajectory models, which identify groups of individuals with similar patterns over time. In order to render participants with and without SPS as comparable as possible, we will calculated propensity scores of SPS and control for them in the statistical analyses using Inverse Probability Weighting. This approach mimics random allocation of exposure and is more rigorous than traditional statistical control. Data will be analysed using logistic or multinomial regression models. Examples of specific questions to be tested are:

1. Are high SPS subjects more likely to frequently (ab)use cannabis than those who are not?
2. Is the association between SPS and cannabis use/abuse comparable in men and women?
3. Does the 5-HTTLPR or other monoamine polymorphisms modulate SPS in cannabis users?
4. Are there interactions between SPS and negative aspects of the social environment (unemployment, financial difficulties, and marital separation) with regard to cannabis frequent use/abuse?
5. Are there three-way interactions between the above-mentioned negative aspects of the social environment, positive aspects of the social environment (social integration and support) and SPS with regard to cannabis frequent use/abuse?

In parallel, data on HPS will be collected among patients (n=100) seeking treatment from addiction structures, with the assistance of the French Fédération Addiction. This will enable to validation of the measure of environmental sensitivity in French, and provide evidence of its acceptability in a clinical setting.

WP1: Task 1.3 Rats [HOMBERG**]**
Rats: First, available data from naïve and cocaine experienced 5-HTT knockout rats (see section 2.1) will be compared to 5-HTTLPR associations in the human cohorts (Task 1.1 and 1.2). Next, we will establish a novel rat model for 'multi-genetic' SPS. Wistar outbred (i.e. genetically heterogeneous) randomized young adult rats are phenotyped according the three of the four SPS facets using the following tests: 1. elevated plus maze, 2. Conditioned freezing, and 3. prepulse inhibition (PPI) [BOX 1; Table 1]. These are relatively short-lasting tests and therefore suited for screening. Since 20% of the human population is high on SPS[1], phenotyping 50 rats per sex provide ~13 low SPS rats, 13 high SPS rats, and 24 'intermediate' SPS rats per experiment. We will make this selection based on a categorization of behavioural outcome measures (Table 1, below): We test male and female rats. We take vaginal smears of the female rats during 1 week before and during testing. The N=13 obtained through this selection procedure will be sufficient, as 12 rats per group are needed for intravenous drug self-administration: power analysis: α = 0.05, 1-β=0.80, effect size=0.55[42]. This takes into account that ~ 20% of the rats may drop-out because of failing catheters.

Table 1 - Test	Procedure	Outcome
1. Elevated plus maze	Rats explore the elevated plus maze for 5 min	Percentage time open arms
2. Conditioned freezing	Rats are presented 5 tones ending with footshock exposure. 24 hrs later 24 tones are intermittently presented in a novel cage	Percentage of conditioned freezing
3. Prepulse inhibition	Rats are exposed to 120 dB startles, some preceded by 3, 5 or 10 dB prepulses above background	Average percentage of PPI

The results are sorted from highest to lowest. For the conditioned freezing and prepulse inhibition tests the top 25% scores are given 3 points, and the 25% lowest scores 1 point. For the elevated plus maze the top 25% scores are given 1 point, and the 25% lowest scores 3 points. The higher the total score, the higher the level of SPS. Points for each test are determined by a factor analysis. 5-HTT knockout rats (showing SPS-like phenotypes, see section 2.1) are used as back-up. After this selection procedure (which will be repeated for every new group) the rats are subjected to the experiments described below. Experiments are executed in a blinded fashion.

Environmental conditions: rats will be:

- socially isolated for 6 weeks prior to the start of the behavioural experiments in type III cages (42 cm long, 26,5 cm wide and 15,5 cm high) without enrichment (social isolation (SI) group; mimicking environmental adversity triggering overstimulation),
- socially housed (4 rats per cage) for 6 weeks prior to the start of the behavioural experiments in type IV cages (60 cm long, 38 cm wide and 20 cm high) with additional toys (social enrichment (SE) group; mimicking a supportive environment). The additional toys will be changed every week during cage cleaning, to create an enriched variable environment.
- socially isolated for 3 weeks, followed by social enrichment for 3 weeks prior to the start of behavioural experiments. This SI + SE group is included to investigate whether a supportive environment remediates the negative effects of an adverse environment

In sum, we use the groups of rats presented in Table 2 (below), each consisting of 26 rats (13 low SPS and 13 high SPS). Since the environmental conditions are applied for several weeks, and the estrous cycle of female rats takes 4-5 days, the females are exposed to the environmental factors across all stages of the estrous cycle. The housing conditions continue during the behavioural experiments below.

Table 2

Group	Housing	Experience	Group	Housing	Experience
1	SI	Naive	4	SI	Cocaine, amphetamine or heroin
2	SE	Naive	5	SE	Cocaine, amphetamine or heroin
3	SI + SE	Naive	6	SI + SE	Cocaine, amphetamine or heroin

Rats are subjected to the behavioural tests below to assess social interaction (SPS facet 4) and cognition. Rats are either decapitated after these behavioural tests (**naïve group**) or subjected to the intravenous drug self-administration paradigm and decapitated afterwards for blood and brain collection (**drug self-administration group**).

Social interaction: Rats are allowed to socially interact with an unfamiliar conspecific of the same group and SPS level for 15 min after 3.5 hrs of social isolation in a test box to which the animals are habituated. Behaviour will be videotaped and prosocial behaviour as well as social avoidance will be analyzed using Observer (Noldus IT) software.

Social preference and memory: Rats are tested in a three-chambered social cognition task, which scores time spent in a side chamber with a novel rat under an inverted wire pencil cup versus time spent in a side chamber with an empty inverted wire pencil cup. Sociability is defined as the subject rat spending more time in the chamber containing the novel target rat than in the chamber containing the inanimate object. The first session takes 15 min and measures whether the target rat prefers a chamber containing a novel rat versus an empty chamber (social preference). After a retention period of 1, 2, 4 and 8 hrs the 15 min test is repeated, and a novel rat is placed beneath the previous empty inverted wire pencil cup. The time spent on exploring the side of the chamber containing the familiar versus novel rat is measured. The more time spent in the chamber containing the novel rat the higher the social memory of the target rat. Behaviour is videotaped during the 15 min sessions and time spent in each compartment and proximity to the pencil cups (with and without rat) is analyzed using Ethovision XT (Noldus IT).

Naïve group: Rats within the naïve group will be decapitated 1 day after the last social test for blood and brain collection and biomarker assessment in WP2.

Intravenous drug (cocaine, amphetamine, cannabinoid or heroin) self-administration group: Rats within the drug self-administration group will be implanted with an intravenous catheter in the jugular vein. After 6 days of recovery, the rats will be allowed access to cocaine (0.50 mg/kg/inj), amphetamine (0.03 mg/kg/infusion), the cannabinoid receptor agonist WIN55,212-2 (0.0125 mg/kg/infusion) or heroin (60 µg/kg/infusion) via a fixed ratio 1 (FR1) lever press response for 1 h/day for 10 days. Blood will be daily withdrawn through the catheters for assessments in WP2. Once rats have acquired drug self-administration, defined as at least 10 reinforced responses over 1 h with less than ± 20% variation in responding from day to day (*regular drug intake*), the rats will be withdrawn for 72 hrs from drug self-administration and tested for social interaction and social preference/memory (see above). The order of the tests will be counterbalanced among the experimental rats. Thereafter the rats get extended access to drug (6 h daily sessions), for a minimum of 15 sessions under an FR1 schedule of reinforcement until drug intake significantly increases (*compulsive drug intake*). Daily blood samples are taken through the intravenous catheter. Then, the animals will the withdrawn again from drug for 72 hrs to subject the animals to the social interaction and social preference/memory tests. Thereafter the animals will be allowed to resume drug self-administration for 6 FR1 sessions of 6 hrs, followed by decapitation at 24 hrs into withdrawal for blood and brain collection and biomarker assessments in WP 2. The dependent measurements include total drug intake over different sessions, intake during the first hour of daily self-administration, and changes in drug-loading behavior (first 10 min interval of exposure to daily drug self-administration). Drug intake will be correlated to SPS levels and the individual SPS phenotypes (table 1). Furthermore, group-wise comparisons will be made according to table 2. The choice for cocaine, amphetamine (representing 'new' stimulant drugs) or heroin will depend on data collected in Task 1.1 and 1.2. The precise drug self-administration regime may be adjusted to the type of drug.

WP2: Task 2.1. Biomarkers of SPS in humans and rat: analyses on blood, saliva and brain [FUMAGALLI].
Blood, saliva and brain material: Blood RNA samples from Task 1.1 and blood samples and brains derived from Task 1.3 will be shipped to Milan. Rat blood will be centrifuged (6500 g for 10 min) to separate plasma and cells. Cells will be used for RNA extraction. Brains will be dissected to collect medial prefrontal cortex, nucleus accumbens, amygdala and insula tissue.

Blood samples: In the rat blood plasma samples we measure the GLU and GABA levels using commercially available ELISA kits (see detailed description below). Additionally, and very interestingly, we will measure crucial determinants that bridge GLU and GABA together such as the levels of circulating GAD and GS. Furthermore, RNA from the human and rat blood cell samples will be used to measure by real time PCR (see detailed description below) GLU and GABA targets that are found to be differentially affected in brains of low versus high SPS rats.

Brain samples: In the rat brains different parameters of the GLN-GLU-GABA cycle will be measured by using real time PCR as well as Western blots (see detailed description below). With respect to the glutamate system, we will measure: vGLUT1 and vGLUT 2, caMKII, NMDA receptors (GluN1, GluN2A, GluN2B), AMPA receptors (GluA1 and GluA2), metabotropic receptors (mGLUR 2/3 and mGLUR5), GLN synthase, the cystine/glutamate antiporter system (xCT), glial transporters EAAT1 and EAAT2. Measures of the GABA system will involve the receptor subunit GABA A receptor, gamma 2 (GABA(A)-γ2) and the GABA-β2/3 receptors, membrane GABA transporters (GAT), the vesicular transporter (Vgat), glutamic acid decarboxylase-65/67 (GAD65/67) and two calcium-binding proteins, parvalbumin and calbindin, which label subgroups of GABAergic interneurons in the prefrontal cortex[53].

RNA Preparation and Real-Time Polymerase Chain Reaction: Total RNA extracted from blood cells and brain tissues of interest will be treated with DNase to avoid DNA contamination. RNA will be then analyzed by a TaqMan qRT-PCR instrument using the iScriptTM one-step RT-PCR kit for probes. Samples will be run in 384 well formats in triplicate as multiplexed reactions. Data will be analyzed with the comparative threshold cycle (ΔΔCt) method using 36B4 as reference gene[55].
Preparation of Protein Extracts and Western Blot Analyses: The brain regions of interest

(see section 2.1) will be extracted and different subcellular compartments will be purified as previously described[55]. Total protein concentrations will be adjusted to the same amount for all samples (10ug per lane) that will be run on a polyacrilamide gel under reducing conditions; proteins will be then electrophoretically transferred onto nitrocellulose membranes. Blots will be then incubated with antibodies against the target proteins using β-actin as the control protein. Immunocomplexes will be visualized by chemiluminescence.

Enzyme-Linked ImmunoSorbent Assay: ELISA kit applies the competitive enzyme immunoassay technique utilizing a monoclonal antibody and the Target molecule conjugated with horseradish peroxidase. The product of the enzyme-substrate reaction forms a blue colored complex. A stop solution is added to stop the reaction, which will then turn the solution yellow. The intensity of color is measured spectrophotometrically at 450nm in a microplate reader. A standard curve is plotted relating the intensity of the color to the concentration of standards. The concentration of the target molecule in each sample is interpolated from this standard curve.

Deliverable	Activity	WP	Task	Month
D1	Report on drug use pathways and associated (social) cognitive, genetic and brain GLU/GLN features as function of SPS level and social environmental conditions in humans	1	1.1	18
D2	Report on relationships between SPS and drug use depending on positive and negative characteristics of individuals' social environment as well as gender.	1	1.2	36
D3	Report on the validity and acceptability of the HSP measure in France.	1	1.2	24
D4	Report on the causal relationship between SPS level, social environmental conditions, social behaviour and pathways to drug use and recovery in rats	1	1.3	30
D5	Report of biomarkers of drug use and recovery pathways as function of SPS and environmental conditions	2	2.1	36

Milestone	Activity	WP	Task	Month
M1	HSP questionnaire data of drug users and controls in ZuCo^{2}St and TEMPO cohorts	1	1.1 1.2	6
M2	Establishment of SPS rat model	1	1.3	11
M3	Analysis of GABA and GLU levels in human blood samples	2	2	19

Grant CHARTT

		1-6	**7-12**	**13-18**	**19-24**	**25-30**	**31-36**	**37-42**	**43-48**
Task 1.1	PhD student	M1		D1					
Task 1.2	PhD student	M1			D3		D2		
Task 1.3	Postdoc 1	Ethical authorization	M2			D4			
Task 2.1	Postdoc 2				M3		D5		
Dissemination	Scientific								
	Public engagement								

4. Information on the project consortium

Please add details for the PI as well as each partner co-PI (max 1 page per CV) and, if applicable, other team members (1/2 page per CV) participating in the project.

PI

Role in Project:	Coordinator		
First Name:	Judith	Surname:	Homberg
With respect to the activities in the project, please provide details of relevant experience and activities within the field of the project	My group has experience with a wide variety of behavioural methods, including intravenous drug self-administration, as well as a wide variety of other behavioural tests. I have strong collaborations with researchers using human subjects, as well as psychiatrists, to foster translational research. In the field of substance use disorders I work with Prof.Dr. Wim van den Brink (e.g., Crunelle et al., 2015, Human Brain Mapping; Kaag et al., 2016, Addiction Biology; Kaag et al., 2016, Am J Psychiatry), based on studies that use parallel and complementary methods in humans and rats. This project will offer me the opportunity to expand my translational research and focus on SPS as source of individual differences in environmental sensitivity.		
With respect to the activities in the project, please provide details of relevant publications in the last five years (maximum of 5)	1. Verheij MM, Vendruscolo LF, Caffino L, Giannotti G, Cazorla M, Fumagalli F, Riva MA, Homberg JR, Koob GF, Contet C (2016) Systemic Delivery of a Brain-Penetrant TrkB Antagonist Reduces Cocaine Self-Administration and Normalizes TrkB Signaling in the Nucleus Accumbens and Prefrontal Cortex. *J Neurosci*. 36(31):8149-59. 2. Van der Doelen R, Kozicz T, Homberg JR (2013). Adaptive fitness: early life adversity improves adult stress coping in heterozygous serotonin transporter knockout rats, *Mol Psychiatry* 18:1244-5. 3. Guidotti G, Calabrese F, Auletta F, Olivier J, Racagni G, Homberg J, Riva MA (2012) Developmental influence of the serotonin transporter on the expression of NPAS4 and GABAergic markers: modulation by antidepressant treatment. *Neuropsychopharmacology* 37(3):746-58. 4. Nonkes LJP, Maes JHR, Homberg JR (2011) Improved cognitive flexibility in serotonin transporter knockout rats is unchanged following chronic cocaine self-administration. *Addiction Biology*, 18(3):434-40. 5. Homberg JR, KP Lesch (2011) Looking on the bright side of serotonin transporter gene variation. *Biological Psychiatry* 69:513-9.		

Role in Project:	Postdoc performing Task 1.2 experiments under supervision of Dr. Homberg		
First Name:	Michel	Surname:	Verheij
Short CV	**Education**: April 2009, PhD in Neuropharmacology (Radboud University Medical Centre, Nijmegen), Thesis title: "Individual differences in the release of newly-synthesisedsynthesized and previously stored accumbal dopamine: a rodent study in low and high responders to novelty". **Research Activity:** Study of individual differences in vulnerability to compulsive psychostimulant self-administration, focus on CRF stress and serotonin systems, as well as psychostimulant mechanisms (monoamine transporter inhibition vs. vesicular monoamine release).		

	Technical skills and competences: Behaviour (elevated plus-maze, fear extinction, pre-pulse inhibition, social interaction, stress models, cognitive tasks drug self-administration, etc.), pharmacology, stereotactic surgeries, catheter implantations, molecular neurobiology, injections, blood samples, brain dissection, etc. **Awards:** Personal ECNP research grant for young scientists in 2013 (50 k€) and fellowship from the NIDA in 2014 to work in the laboratory of Prof.Dr. George Koob (80 k€) Michel Verheij is author of 25 peer review papers and published, amongst others, in Journal of Neuroscience, Psychopharmacology, Neuropsychopharmacology, and Addiction Biology (3 last author papers)

Co-PI 1

Role in Project:	Group Leader and expert in molecular analyses		
First Name:	Fabio	Surname:	Fumagalli
With respect to the activities in the project, please provide details of relevant experience and activities within the field of the project	My group has experience with a wide variety of molecular techniques to measure changes in gene and protein expression. We can measure the steady-state levels of proteins but also the dynamics of trafficking and/or redistribution by purifying specific subcellular compartments such as nuclear, cytosolic and membrane fractions. I have valid collaborations with people using behavioral tests that con complement our analyses. This project will allow me to expand my knowledge, fruitful collaborations as well as have access to translational research.		
With respect to the activities in the project, please provide details of relevant publications in the last five years (maximum of 5)	1. Caffino L, Racagni G and Fumagalli F (2011) Stress and cocaine interact to modulate Arc/Arg3.1 expression in rat brain *Psychopharmacology*, 218: 241-248. 2. Giannotti G, Caffino L, Calabrese F, Racagni G, Riva MA and Fumagalli F (2014) Prolonged abstinence from developmental cocaine exposure dysregulates BDNF and its signalling network in the medial prefrontal cortex of adult rats. *International Journal of Neuropsychopharmacology*, 17(4): 625-634. 3. Caffino L, Frankowska M, Giannotti G, Miszkiel J, Sadakierska-Chudy A, Racagni G, Filip M and Fumagalli F. (2014) Cocaine-induced glutamate receptor trafficking is abrogated by extinction training in the rat hippocampus. *Pharmacological Reports* 66: 198–204. 4. Caffino L, Calabrese F, Giannotti G, Barbon A, Verheij M, Racagni G and Fumagalli F (2015) Stress rapidly dysregulates the glutamate synapse in the prefrontal cortex of cocaine-withdrawn adolescent rats. *Addiction Biology*, 20:158-169, 2015. 5. Caffino L, Giannotti G, Malpighi C, Racagni G and Fumagalli F (2015) Short-term withdrawal from developmental exposure to cocaine activates the glucocorticoid receptor and alters spine dynamics *European Neuropsychopharmacology* 25:1832-4.		

Role in Project:	Postdoc performing Task 2 experiments under supervision of Prof.Dr. Fumagalli		
First Name:	Lucia	Surname:	Caffino
Short CV	**Education**: December 2010, PhD in Pharmacology and Biotechnology (University of Milan), Thesis title: "Modulation of neuroplastic mechanisms by acute and chronic exposure to		

	cocaine". **Research Activity:** Analyses of the mechanism of action of drugs of abuse, mainly the psychostimulant cocaine, during adolescence, a period of high vulnerability. Main goal is to identify molecular targets in the short- and long-term abstinence from adolescent psychostimulant exposure. **Technical skills and competences:** Major techniques in Molecular Biology and Biochemistry Animal handling (rodents), injection (subcutaneous, intraperitoneal), blood sampling, brain areas dissection techniques. **Awards:** Winner of Scholarship to participate at the Summer Course "Cellular Biology of Addiction", Barcelona 13-20 July 2014 Lucia Caffino is author of 30 peer review papers and published, amongst others, in Psychopharmacology, Neuropsycho-pharmacology, and Addiction Biology

Co-PI 2

Role in Project:	Group leader in social epidemiology in the area of substance use		
First Name:	Maria	Surname:	Melchior
With respect to the activities in the project, please provide details of relevant experience and activities within the field of the project	My group has extensively studied the role of different aspects of the social environment with regard to trajectories of substance use – including cannabis, particularly during the period of transition from adolescence to young adulthood. We have shown the extent of social inequalities with regard to substance use in this period, as well as the importance of social relations with family and friends. We also have a special interest in the heightened vulnerability of women with regard to substance use.		
With respect to the activities in the project, please provide details of relevant publications in the last five years (maximum of 5)	1. Melchior M. Cannabis abuse from one generation to the next-a heightened vulnerability in women? *Addiction*. 2015;110:1118-9. 2. Melchior M, Chollet A, Elidemir G, Galéra C, Younès N. Unemployment and substance use in young adults: does educational attainment modify the association. *European Addiction Research*, 2015;21(3):115-123. 3. Melchior M, Prokofyeva E, Younès N, Surkan P, Martins S. Treatment for illegal drug use disorders: the role of comorbid mood and anxiety disorders. *BMC Psychiatry* 2014;14:89. 4. Bowes L, Chollet A, Fombonne E, Galéra C, Melchior M. Lifecourse SEP and cannabis use. *European Journal of Public Health*, 2013; 23(2):322-327. 5. Redonnet B, Chollet A, Fombonne E, Bowes L, Melchior M. Tobacco, alcohol, cannabis and other illegal drug use among young adults in France: the socioeconomic context. *Drug and Alcohol Dependence*, 2012;121(3):231-239.		

Role in Project:	Statistician preparing the TEMPO database for analyses under supervion of Dr. Melchior		
First Name:	Camille	Surname:	Bolze
Short CV	**Education**: May 2013, Master's in Public Health **Research Activity:** Responsible for data management, statistical analyses and internal as well as external communication activities for the TEMPO study since 2015. **Technical skills and competences**: Data management, statistics.		

Role in Project:	Project manager at Fédération Addiction (Task 1.2)		
First Name:	Laurène	Surname:	Collard
Short CV	**Education**: May 2011, Master's in Political Science **Research Activity:** Responsible for international collaborations and network mobilization for the French Fédération Addiction. **Technical skills and competences**: Project management.		

A PhD student will be recruited to conduct the planned statistical analyses, if the project is funded.

Co-PI 3

Role in Project:	Group leader and expert in drug use disorders		
First Name:	Boris B.	Surname:	Quednow
With respect to the activities in the project, please provide details of relevant experience and activities within the field of the project	We are investigating the interplay between drug use and information processing, cognition, personality, genes, and social environment in order to differentiate predisposing factors from consequences of drug use. Only with this information we will be able in the future to improve prediction and prevention of drug use and addiction and we can identify treatment targets for pharmacological and psychotherapeutical approaches.		
With respect to the activities in the project, please provide details of relevant publications in the last five years (maximum of 5)	1. Havranek, M. M., Vonmoos, M., Muller, C. P., Buetiger, J. R., Tasiudi, E., Hulka, L. M., Preller, K. H., Mossner, R., Grunblatt, E., Seifritz, E., & Quednow, B. B. (2015) Serotonin Transporter and Tryptophan Hydroxylase Gene Variations Mediate Working Memory Deficits of Cocaine Users. *Neuropsychopharmacology*, 40(13):2929-2937. 2. Hulka, L. M., Scheidegger, M., Vonmoos, M., Preller, K. H., Baumgartner, M. R., Herdener, M., Seifritz, E., Henning, A., & Quednow, B. B. (In Press) Glutamatergic and neurometabolic alterations in chronic cocaine users measured with H-magnetic resonance spectroscopy. *Addict Biol*. 3. Hulka, L. M., Treyer, V., Scheidegger, M., Preller, K. H., Vonmoos, M., Baumgartner, M. R., Johayem, A., Ametamey, S. M., Buck, A., Seifritz, E., & Quednow, B. B. (2014) Smoking but not cocaine use is associated with lower cerebral metabotropic glutamate receptor 5 density in humans. *Mol Psychiatry*, 19(5):625-632. 4. Vonmoos, M., Hulka, L. M., Preller, K. H., Jenni, D., Baumgartner, M. R., Stohler, R., Bolla, K. I., & Quednow, B. B (2013) Cognitive dysfunctions in recreational and dependent cocaine users: role of attention-deficit hyperactivity disorder, craving and early age at onset. *Br J Psychiatry* 203(1):35-43. 5. Vonmoos, M., Hulka, L. M., Preller, K. H., Minder, F., Baumgartner, M. R., & Quednow, B. B. (2014) Cognitive impairment in cocaine users is drug-induced but partially reversible: evidence from a longitudinal study. *Neuropsychopharmacology* 39(9):2200-2210.		

The PhD student who will perform Task 1.1 studies will be defined when this proposal has been accepted.

5. COST CALCULATION

Please add the financial summary for each project consortium partner and, in accordance to relevant national/regional eligibility rules, justify the resources to be committed.

PI

Organisation name: Radboud University Medical Centre **Country:** The Netherlands		**Please indicate if the costs are listed with or without taxes according to the national funding rules (eligible costs) of your country: with taxes**				
		Year: 11/2017 to 4/2018	Year: 5/2018 to 4/2019	Year: 5/2019-10/2019		**Total:**
Project costs per Partner in €	Personnel (postdoc; 1 fte/month)	32.000	65.000	33.000		130.000
	Overhead					
	Travel & subsistence	5.000	1.500	1.500		8.000
	Equipment					
	Consumables	10.000	17.000	10.000		37.000
	Other costs					
	Subcontracting					
	Total costs	47.000	83.500	44.500		175.000
Financing per Partner in €	**Funding requested**					175.000
	Co-financing					
	Co- financing: Please describe how you plan to finance costs -not covered by funding organisations participating in this call (e.g., by internal funds) :					
	The PI's travel costs will be covered by structural income of the research group. All equipment (e.g. self-administration cages) needed for the proposed experiments is available, funded by Investment grants (e.g. Province Gelderland). A technician, who is already paid, will support the postdoc who will performed the proposed experiments.					
Nature, name and address of subcontractors	n/a					

Personnel Costs	Costs involve 1 fte postoc for 2 years. The intended postdoc is Dr. Michel Verheij (Nijmegen, NL), available by November 2017.
Equipment	All equipment is available, no additional costs are involved

Consumables	Consumables involves the housing and care of animals, according to integral costs of the university. Other consumables involve cocaine and surgery needs
Travel	3.000 in total for the postdoc to visit partners and have consortium meetings. The PI will fund own travel from internal funds. The PI will organize the kick-off meeting in funding year 1, for which 5.000 euro is reserved. This budget can cover the catering and travel costs/housing of Dr. Pluess, Mr. Van Den Anker and Ms. Collard. PIs and researchers working on this project will pay own travel costs. By using a university room, there will be no costs for the venue.
Subcontracting	n/a
Other costs	

CO-PI 1

Organisation name: Department of Pharmacological and Biomolecular Sciences, University of Milan **Country:** Italy		**Please indicate if the costs are listed with or without taxes according to the national funding rules (eligible costs) of your country: with taxes**				
		Year: 5/2017 to 4/2018	Year: 5/2018 to 4/2019	Year: 5/2019-4/2020		**Total:**
Project costs per Partner in €	Personnel		25.000	25.000		50.000
	Overhead		5.000	5.000		10.000
	Travel & subsistence		3.000	8.000		11.000
	Equipment					
	Consumables		42.000	37.000		79.000
	Other costs					
	Subcontractors					
	Total costs		75.000	75.000		150.000
Financing per Partner in €	**Funding requested**		50.000	50.000		100.000
	Co-financing		25.000	25.000		50.000
	Co- financing: Please describe how you plan to finance costs not covered by funding organisations participating in this call (e.g., by internal funds) :					
	A postdoc paid by funding from the University of Milan (Dr. Lucia Caffino) will perform the experiments. All equipment needed for the proposed experiments is available in the Department of Pharmacological and Biomolecular Sciences.					
Nature, name and address of subcontractors	n/a					

Personnel Costs	n/a
Equipment	All equipment is available, not additional costs
Consumables	General chemical reagents; RNA extraction kits; primary and Secondary Secondary antibodies; western blotting reagents; kits for RNA retrotranscription; kits for Real Time PCR; kits for the determination of corticosterone as well as glutamatergic and GABAergic determinants in the blood

Travel	3.000 in total for Co-PI and postdoc travels to visit partners and have consortium meetings. In funding year 3, we request 5.000 euros to organize the midterdm meeting in Paris (costs for Dr. Pluess, Mr. Van Den Anker and Ms. Collard will hereby we covered).
Subcontracting	n/a
Other costs (Indirect costs)	n/a

CO-PI 2

Organisation name: INSERM **Country:** France	Please indicate if the costs are listed with or without taxes according to the national funding rules (eligible costs) of your country: with taxes				
	Year: 5/2017-4/2018	Year: 5/2018-4/2019	Year: 5/2019-4/2020		**Total:**
Personnel: statistician PhD student	46.950 33.800	46.950 33.800	 33.800		195.300
Overhead	6.000				6.000
Travel & subsistence	1.000	5.000	1.000		7.000
Equipment					
Consumables					
Other costs	28.100				28.100
Subcontractors	15.000				15.000
Total costs	130.850	85.750	34.800		251.400
Funding requested	97.050	51.950	1.000		150.000
Co-financing	33.800	33.800	33.800		101.400
Co- financing: Please describe how you plan to finance costs not covered by funding organisations participating in this call (e.g., by internal funds) :					
Funding for a PhD student (approximately 101.400 euros) will be sought from other sources such as university funding.					
Nature, name and address of subcontractors	N/A				

Personnel Costs	Costs involve the salary of Camille Bolze, the TEMPO study statistician for 14 months in order to prepare data collection activities, set up the database and conduct preliminary statistical analyses which will be completed by a PhD student.
Equipment	No particular equipment is necessary for the conduct of this project.
Consumables	N/A
Travel	The total cost of travel to consortium meetings for Camille Bolze and the PhD student who will be recruited is estimated at approximately 1.000 euros in funding years 1 and 3. Maria Melchior will fund her travel from internal funds. In funding year 2, we request 5.000 euros to organize the midterdm meeting in Paris (costs for Dr. Pluess, Mr. Van Den Anker and Ms. Collard will hereby we covered).
Subcontracting	The cost of involving the Fédération Addiction (represented by Mrs. Laurène Collard, responsable for international collaborations) in the project is estimated at 15.000 euros – which covers the salary of Mrs.

	Collard (8.000 euros), the cost of organizing meetings with health professionals to validate the French version of the SPS questionnaire among patients of addiction treatment centers (2.000 euros), and the cost of disseminating research findings to health professionals via a small brochure and through in-person meetings (5.000 euros).
Other costs (Indirect costs)	Data collection costs associated with the assessment of Sensory Processing Sensitivity (SPS) among 1400 TEMPO participants as well as a sample of 100 patients are estimated at a total of 11.400 euros: preliminary mailing + postal verification to identify TEMPO participants' current address (3.000 euros); set up of Internet questionnaire and website fees (1.300 euros), printing and mailing of a postal questionnaire with 2 recalls (2.100 euros), monetary incentives for participating patients (2.000 euros), data entry of paper-and-pencil questionnaires (3.000).

6. Impact of the project and engagement in responsible research and innovation

6.1 How will the outcomes of the project provide relevant information for policy-making and society (max. 1 page)?

Our approach is envisioned to bring together resources and knowledge across different fields, technologies and disciplines. This will cover activities from research to, potentially, market with a new focus on innovation-related activities.

Drug use represents one of the actual major public health issues with significant social and economic impacts on our society. Drug use not only has a serious negative impact on individuals' health, including addiction and dependence-induced diseases like cardiovascular illness, viral infections including HIV, mental disorders etc. but it also leads to social problems and adverse consequences including the division of families, tragic accidents, the reduction of work performance, crime and violence. There are more than a billion people worldwide using various drugs at an enormous cost to society. Yet there is currently limited understanding of effective ways of reducing drug use and assisting drug users (especially those using stimulants and cannabis) aiming for recovery.

The possibility that social environmental factors influence pathways to drug use and recovery in high SPS individuals – as supported by biomarkers and animal studies - may represent a unique opportunity to link social and scientific issues. Dr. Michael Pluess (Queen Mary University of London, UK; SPS expert), Mr. Marcello Van Den Anker (drug use expert and leading an agency supportino drug users to recover) and the French Fédération Addiction will give advice regarding study designs which we will implement when we start our studies, and potentially help to adjust study aims during the project when needed. Furthermore, the potential of the collected data to formulate recommendations for interventions to reduce drug use will be directly considered. Dr. Pluess is well qualified for this task as he successfully developed an intervention to reduce depression scores in high SPS children living in deprived neighborhoods[10]. Mr. Marcello Van Den Anker represents the drug users 'from the street' , has a great sense of social environmental factors that play a key role in the lives of drug users and extensive contact with drug users as well as organizations helping homeless and drug users. SPS is easily recognizable and its assessment early on in life in populations living under poor socioeconomic conditions may be a cost-effective method to identify individuals who most likely benefit from programmes promoting emotional reslience and aiming to reduce drug use and increase recovery.

The French Fédération Addiction is a civil society structure which brings together structures involved in the treatment and support of people with addiction in France and aims to adapt and improve professional practices of health professionals, social workers, and other professionals in contact with people who use substances. The collaboration with this partner will make it possible to verify the acceptability of the concept of SPS among users and professionals in contact with them, as well as directly disseminate research findings to those most directly affected by drug use.

In section 6.2 we further describe our dissemination activities.

6.2 Description of how the consortium will engage with societal actors during and after the research process and how they will develop outreach and dissemination activities during and at the end of the project to ensure the widest transfer of the produced knowledge (max.3 pages).

While our project STANDUP addresses precise scientific goals, disseminating the results to a wider audience will be important to maximise the strategic impact of the project. Therefore, disseminating knowledge from this project will follow a six-fold process.

- We will disseminate our findings to the public through HSP societies and websites (e.g., website of Dr. Elaine Aron: http://hsperson.com/). Dr. Homberg has contact with Dr. Elaine Aron who introduced the SPS concept with whom they wrote a joint review on the topic[57]. Through interaction with Mr. Marcello Van Den Anker (http://www.bureau-marcello.nl) data collected within this project can be spread to drug users. Furthermore, outreach to the general public will be done by organizing presentations at open days of the participating institutes, like the 'Donders Open Day', 'Brain Awareness week' and the "Long Night of Sciences" regularly organized in several European cities, and the "Public day" which is offered by the ECNP at its annual meetings. In frame of the BrainFair convention of the University of Zurich and the ETH, Prof.Dr. Quednow gives lectures for school classes on drug use in the adolescence. Dr. Fumagalli is also well involved in disseminating the results of his research, primarily among adolescents. Furthermore, he is part of the CEND (Center of Excellence on Neurodegenerative Diseases) (http://www.cend.unimi.it/it/) which organizes every year the so called 'Brain Awareness week' and organizes conferences and lectures. The CEND has an active programme of continuous education, with different initiatives, such as the so-called 'Intinerars in Neuroscience', which consists of a series of lectures held by researchers among the most active and advanced in the field of neurosciences in the world. Dr. Melchior will work jointly with the French Fédération Addiction to disseminate the results of this project to professionals involved in the treatment of individuals with addictive behaviors, as well as to the general population (through the Fédération Addiction website, a specific brochure, training sessions and seminars for professionals). Finally, we will also disseminate our findings to the public through our departmental websites and appropriate contributions to mainstream media with the assistance of university press offices. As part of their commitment to public engagement in science the partners regularly deliver public lectures and tutor school students on drug use epidemiology, neuroscience and neuropsychiatric topics.
- Fundamental scientific results will be freely disseminated through appropriate channels: scientific publications, and presentations at international conferences (e.g. SfN, FENS, EBPS, AGNP, DNM, ECNP meetings). Moreover, all partners have agreed to release information without any delay. Wherever possible and appropriate young partners will be encouraged to present the results, thereby enhancing their confidence and visibility. The financial support from *ERANID* will be acknowledged in all dissemination activities (open access scientific papers, workshops, leaflets, reports, etc). The following text will appear in all our publications: "This study has been carried out with the financial support of *ERANID*".
- To disseminate findings to stakeholders Dr. Homberg has contact with Dr. Michael Pluess who will give addice for experimental designs and help in the evaluation of our data and their potency to come to recommedations for interventions to reduce drug use in high SPS subjects. Dr. Homberg is furthermore member of a novel consortium, the UK biobank for environmental sensitivity led by Dr. Michael Pluess and Prof. Elaine Fox (UK). Dr. Homberg has also contact with Mr. Marcello Van Den Anker who could implement aspects of our findings in his drug user support and advice activities. Also Homberg's contact with Denise Jonkers, a psychologist having high SPS people as clients (e.g. http://www.ontwikkelingswerkplaats.nl/), allows dissemination of findings. Finally, Dr. Melchior has contact with the French Fédération Addiction which can use the findings of this study to help drug addicts to recover. Other stakeholders will be informed by our scientific publications and newletters.
- Physicians will be informed through publications in laymen language as well as general medical journals in the field, newsletters, and presentations at clinical meetings (in France this will be largely achieved through the collaboration with the Fédération Addiction). As these professionals are busy we will develop "science blitz" updates on

the latest research in these clinical articles. We will also use our personal contacts to inform physicians. For instance, Dr. Homberg has contact with Nijmegen Institute for Scientist-Practioners in Addiction (NISPA; http://www.nispa.nl/home) on whose behalf she teaches postdoctoral addiction practioners. Furthermore, Prof.Dr. Quednow has a large network with psychiatrists and hospitals specialized in drug addiction, were he recruits study participants and were he also regularly teaches recent advances in addiction research and medicine. Finally, Dr. Fumagalli will organize and promote seminars and debates in Lombardy and other regions of Italy by recruiting experts such as psychologists, psychotherapists and other physicians.

- We will also disseminate to the patient community and associations for subtance use disorders. Prof.Dr. Quednow has regular contact with several types of drug prevention organisations such as the Streetwork departments of the cities of Zurich, Bern and Biel, Eve and Rave, Saferparty, Rave it Save and so on. Furthermore, we inform these associations through layman newsletters.
- Policy makers are amongst the most difficult groups to approach. However, Prof.Dr. Quednow is member of the the Swiss Society of Addiction Medicine and has a close collaboration with the Swiss Institute of Addiction and Health Research, which is focussed on prevention and intervention at the societal level. Furthermore, he is sitting in the scientific board of the NGO "Dr. Sexual Health" for drug-related risks. Additionally we will modify the “science blitz” content for policy makers (and other laymen) to provide policy makers with science-driven knowledge in a fast and well-marketed way, and we will engage in direct lobbying by sending out newsletters and updates in a crisp manner.

The table below provides an overview of dissemination tools we will implement, supported by communication departments of our universities:

Target audience	Key messages/information	Dissemination tools
General public	• Increase public awareness of the relationship between SPS, environment and drug use	Messages on HSP websites, institutional websites, Intervention in mass media (press releases, events), presentations at public meetings
Scientific community	• To inform scientists across disciplines (psychology, neurobiology, clinical medicine, psychiatry)	Open access scientific journals, newsletters, presentations at national and international meetings, organisation of an international conference
Stakeholders	• To coordinate activity, promote collaboration and facilitate interpretation of results	Personal contacts, Scientific journals, newsletters
Physicians	• Recommendations for promoting healthier habits to deal with overstimulation	Personal contacts, teaching, Newsletters, Science Blitz, medical journals, presentations at clinical meetings
Patients	• To create awareness on relationship between SPS and substance related disorders • Recommendations for promoting healthier to deal with overstimulation	Personal contacts with associations, Patient association newsletters
Policy makers	• To create awareness on relationship between SPS and	Existing collaborations and membership of boards, Lobbying,

	drug use • To creative awareness of the impact of environmental factors on mental health	science blitz

As a wide range of dissemination measures is foreseen, a Plan for Using and Disseminating Knowledge (PUDK) will be implemented at the beginning of the project, summarizing the strategy and the concrete actions for the protection, exploitation and dissemination of the results. Dissemination and use of knowledge will be addressed and progressively developed throughout the project and mainly at the end of the project (see timeline section 3.0), for pursuing the use and dissemination of knowledge.

Opportunities for the dissemination and exploitation of results may present also after the end of the funding period of our *ERANID* project. In particular, the opportunity of a real-life intervention aiming to address the specific needs of individuals who use drugs according to their levels of SPS will be ascertained during and at the end of the STANDUP project (for instance in France where contacts established with professionals via the Fédération Addiction will result in strong interplay between researchers and practionners). This is why our STANDUP consortium will not be disassembled after the 3-year period, and will continue to organise ad hoc meetings whenever called for (see timeline section 3.0). We expect that the STANDUP partners will form and/or retain collaborations beyond the funding period of the *ERANID* project. As we are collaborating also by other means (see section 2.5), this is a feasible objective.

6.3 Description of how ethical issues of the project proposal will be tackled - especially when dealing with vulnerable groups - to ensure quality and integrity of the research (e.g. by adopting existing codes of ethical conduct in research). When applicable, ethical and legal issues (e.g. informed consent, ethical permits, data protection) should comply with national regulations (max. 1 page).

Research to identify the biological basis of behavioral traits and mental health is extremely sensitive. The researchers are aware of the ethical issues concerning privacy and confidentiality, the psychological impact on participating individuals, data protection, etc. and will respect official guidelines.

The European Guidance for Healthcare Professionals on Confidentiality and Privacy in Healthcare and the Directive 95/46/EC (and its revision) on the protection of individuals with regard to the processing of personal data and on the free movement of such data will be respected, as will Article 29 workgroup paper n°WP131 on the processing of data from electronic health records, and all study procedures will follow this guidance.

The ZuCo^{2}St (KEK-ZH-Nr. E14/2009) and opioid (KEK-ZH-Nr. 2015-0238) cohort studies have been approved by the Cantonal Ethics Committee of Zurich. All participants provided written informed consent and received compensation for their participation. The ethical application for the cannabis study will be submitted until end of 2016. Furthermore, all TEMPO study participants have expressed informed consent to participate in the study and specifically contribute salivary samples that were used to test for genetic markers related to behavior and substance use. The TEMPO cohort study was approved by France's institutions overseeing ethical data collection in health research (CCTIRS: Comité Consultatif pour le Traitement des Informations pour la Recherche en Santé; CNIL: Commission Nationale Informatique et Liberté). There are multiple approval codes; these can be provided upon request. All statistical analyses that will be conducted will be approved by the CCTIRS and the CNIL. Furthermore, all relevant regulatory authorities in France will be informed prior to the implementation of the HSP questionnaire among patients, in order to garantee ethical research conditions.

Animals are used to provide a causal relationship between social environmental factors, SPS and drug use. We also collect brain tissue, which cannot be obtained from human subjects. Rats are chosen as they have an elaborative behavioural repertoire, are social and are most suitable for the intravenous drug self-administration model. The animal experiments planned in the framework of this project are performed following the local legislation in The Netherlands, which has been modified according to the Directive 2010/63/EU revising Directive 86/609/EEC on the protection of animals and are covered by an approval of the Dutch national ethical committees in The Netherlands. We will start writing the ethical permit as soon as we have been informed out the outcome of the evaluation of this proposal. For this reason Task 1.3. begins 6 months after the start of the project. We will not proceed with any research with ethical implications before the *ERANID* has received a scanned copy of all documents proving compliance with existing EU/national legislation on ethics. Since we received ethical approval for comparable rat studies previously we do not foresee problems with obtaining ethical permission. The researchers and supprting staff involved all have their article 9 status, a personal license to work with animals. The three R's (Replacement, Reduction and Refinement) will be taken into account, and we will make a careful weighting between the relevance of the outcome of the animal study, and the animal suffering.

A Consortium Agreement will be drafted (adopted from the DESCA-2020 model of the EU program Horizon 2020) and signed by all partners, which will cover responsibilities of parties involved and liabilities towards each other, governance structure, financial provisions, and the handling of intellectual property rights and patenting issues.

All study results will be disseminated to the scientific community and a wider public (via the standard means of publications, internet, congresses and meetings). We opt for open access publications. Final data collected by this project will be shared in a timely fashion, after the main findings have been published. The precise content of the data sharing plan, and its mode (e.g., either responding directly to data requests or by delivering data to a data archive) will be elaborated. Identifiers will be removed from the data prior to release for sharing. A data-sharing agreement will be drafted including restrictions against attempting to identify study participants, a commitment to data protection, requirement of destruction of the data after analyses are completed, reporting responsibilities, restrictions on redistribution of the data to third parties, and proper acknowledgement of the data resource.

6.4 Description of the way the gender dimension will be dealt with by fostering gender balance in research teams and integrating the gender dimension in research content to improve quality and societal relevance and expected results (max. 1 page).

Our consortium consists of two female (Homberg, PI; Melchior; Co-PI) and two male researchers (Quednow and Fumagalli, Co-PIs).

Moreover, the TEMPO, ZuCo^{2}St, opioid, and cannabis cohort studies consist of male and female subjects. Although SPS is equally seen in men and women[1], men may more often use drugs to deal with overstimulation. STANDUP will reveal whether the latter is supported by data. If so, boys high on SPS may particularly benefit from supportive social environmental stimuli to prevent and reduce drug use. Nonetheless, preferably both boys and girls should be supported as in girls exposure to beneficial environmental stimuli also the incidence of depression may be reduced[10]. Hence, the impact of a supportive environment in high SPS individuals may be broad, and go beyond drug use. In fact, since substance use disorders are often comorbid with major depressive disorder[56], reducing the incidence of one may consequently decrease the incidence of the other. As depression scores are available in the ZuCo^{2}St, cannabis, and TEMPO cohorts, we have the opportunity to explore whether gender in high SPS subjects is differentially associated with drug use pathways and depression. In the rat studies we also test male and female subjects. While in humans gender-related biological and cultural factors can influence drug use, in rats we study biological factors only. This allows us to determine the contribution of gender-related biological versus cultural factors to drug use and recovery in high SPS individuals.

STANDUP agrees that the potential diversity and richness of European research will only be fully accomplished if maximum use is made of the pool of human resources and talents available. This therefore implies adopting measures that promote women within their scientific career. Women are directly involved both in the scientific management of STANDUP since the scientific leadership is held by a woman scientist.
In particular, the partners will promote equal opportunities by:

- Making sure that at least 1/3 of researchers employed on this project are female, preferably more.
- Increasing organisational awareness of the importance of gender equality in research structures; Initiating flexible working hours and other family-friendly policies. Notably, Dr. Homberg is chair of the Gender Workgroup of the Donders Institute for Brain, Cognition and Behaviour in Nijmegen, where she is influential on the implementation of such activities.
- Arranging that STANDUP meetings do not to fall on the day before or after the weekend to avoid travelling during weekends in an effort to create a positive work-life balance.

Among the considerations that need to be taken into account to favour gender equality, is the need for flexible working patterns for women (and for men), to facilitate childcare arrangements. Flexible working patterns are commonly accepted in European research institutions and will be the rule in the STANDUP consortium. Another factor to promote the advancement of women is the measure for the reintegration of female (and male) researchers, who have taken time off to raise families. The implication is that part-time scientific career possibilities will be provided at all levels for working mothers.

6.5 Description of how intellectual property rights will be handled (e.g. any barriers to sharing materials or results), both within and outside the research consortium. Please include background and foreground information to help understand your starting intellectual property position and place that in context with any intellectual property that may be generated during the research (max. 1/2 page).

There are no a priori intellectual property (IP) issues in this project. Yet, research activities carried out under this research program might have intellectual property impact. For example, candidate biomarkers relevant for predicting pathways to drug use and recovery in association with human traits and social environmental factors could be identified. The partners will identify potential results that should be considered for IP protection and/or exploitation by screening deliverables, planned publications and annual progress reports. Furthermore, systematic internal review of unpublished data will be performed to detect at an early stage the most (socially and industrially) exploitable research results. The IPR (intellectual property rights) related to these discoveries will be protected by filing patent application forms under the responsibility of the relevant participant notifying the coordinator who will inform *ERANID*. Each participant will pass on each planned publication with a preliminary advice regarding the opportunity to protect the results to its technology transfer body of their respective Institutions.
This expert personnel will recommend an IPR protection strategy that addresses the objectives of both rapid public dissemination and optimal protection of results. It will be up to each concerned partner to protect their IP in the way they deem the most relevant.

7. Additional information

Any additional information requested by specific national funding bodies.

Project coordination and management

The project will be managed by all partners together and co-ordinated by Dr. Judith Homberg. Once funding has been granted, a common start date will be found together with all partners and national funding institutions in 2017, most likely May 2017. Before this date a Consortium Agreement will be drafted and signed by all partners, which will contain the project start date and manage the delivery of project activities, finances, and intellectual property rights. In the first weeks after this date, a Kick-Off Meeting (Nijmegen) will be scheduled for all partners, Dr. Pluess, Laurène Collard of Fédération Addiction, and Mr. Marcello Van Den Anker (stakeholders) during which details of the project will be discussed including the social factors to be included in data anlyses, exchange of data, biological material and personnel. In monthly telephone or skype conferences, the progress of all analyses and experiments will be discussed among all partners and decisions about next steps will be taken. After about 18 months of funding a Midterm Meeting (Paris) will be held to which all participating scientists and stakeholders will be invited. The progress of STANDUP will be monitored by presentations of the data of each group and possibly necessary adjustments to the project plan will be discussed and decided. Moreover, first publications and patent filings will be planned. In a Final Meeting (Milan) after about 33 months of funding, again all scientists and stakeholders will be invited. The scientists present their data and publications and patents will prepared.

The coordinator will be responsible for the communication and reporting to the Joint Call Secretariat. The other partners will submit reports separately to their national funding organization, if necessary. The coordinator and, if requested, some of the other partners will present the progress of the consortium at the intermediate and the final status symposium of STANDUP.

Young scientists (postdocs and PhD student) involved in STANDUP will get opportunities to travel between the partner labs and get training in the different scientific approaches and technologies available there. STANDUP will install a website with an internal part only accessible by participants to store and share data and a public part which will present the consortium to the outside world.

Risks and contingency plan

As part of the management activities in STANDUP, a risk management plan will be drawn up at project start. This risk management plan will outline the procedure for managing risks in the project. The plan will contain a risk register (based on what is outlined below) so that the partners can follow the risks, the probability they may arise and the corresponding response to the risk or strategy for risk avoidance. For each risk identified, a STANDUP partner will be given the responsibility for following the risk and for informing the other partners of any change in the probability the risk may arise and the appropriate strategy for dealing with it. Partners will be asked to identify new risks on a regular basis and discuss them at project meetings to get the most appropriate response.

Potential risks	Mitigation means
Task 1.1: Delay in the collection of HSP questionnaire data of cohort subjects	As explained in section 3.0, we have the alternative to use proxies of items in this questionnaire based on other questionnaire information already available
Task 1.2. Delay in the collection of HSP questionnaire data among TEMPO cohort subjects and patients	Among TEMPO study participants we have the alternative to use proxies (genetic and based on questionnaire data) that are already available; among patients we will be able to qualitatively ascertain the acceptability of the questionnaire
Task 1.3: Failure of establishment of SPS rat model	We use 5-HTT knockout rats displaying high SPS features and their wild-type counterparts as alternative. Data on cocaine and amphetamine self-administration in these rats

	that are available will be complemented by experiments in which the social conditions (social isolation, social enrichment) are manipulated and social interaction/cognition tests are implemented in the experimental design (see section 3.0). In parallel, 5-HTTLPR genotype will be implemented in Task 1.1. and 1.2.
Task 2: Relevant number of samples to be managed by Co-PI 1 for studies on gene expression may slow down the time necessary to get results	The laboratory of Co-PI 1 is fully equipped with respect to RNA extraction and processing since it is available the Tissue Lyser from Qiagen that allows to homogenate the brain areas of interest in 30 seconds. Commercially available, standardized kits allow to obtain total RNA within an hour. Co-PI's 1 lab recently purchased the Biorad CFX384 real-time PCR detection system, that allows to process as many as 384 replicates in a single run (1.5 hour), i.e. an estimate of 100 samples in a single run. It is believed this approach should significantly shorten the time to get informative data on the investigated genes under the different experimental conditions.
Task 2: Relevant number of samples to be managed by Co-PI 1 for studies on protein expression which may slow down the time necessary to get results	Attention will be focused on those proteins whose genes are altered following the first screen done by RT-PCR. Thus, selected western blots will be run and selected ELISA experiments will be performed.
There are three main risks regarding the project administration: • delay in the project progress • delay in the reporting • over or under-spending of resources	These risks will be mitigated by the development of a risk management plan whose aim is to identify and assess risks in order to diminish their likelihood or exposure.

Taking into account these different strategies to prioritize and optimize our research, we have the feeling that these limitations will be potential in nature but will not compromise the success of our global approach.

8. Checklist for Proposals

The proposal conforms to the Guidelines for Applicants.	X
Every project partner has checked that their collaboration and their project contribution is eligible for funding.	X
All partners who are not eligible for 100% funding are able to provide financial resources for their own contribution.	X
The consortium is aware of the necessity to have a consortium agreement, including amongst others the agreements on intellectual property rights (IPR) and publication rules for a funded project (depending on the national/regional regulations).	X

9. Declaration

I the undersigned, hereby quote to supply the goods / service / products detailed in this call, at the respective prices quoted.

I certify that as far as I know, the information I have supplied is accurate.

I agree that the funding agencies may discontinue the call arrangements at any time before a proposal has been accepted.

I understand that the funding agencies are not bound to accept any proposal and will not be liable under any circumstances whatsoever for the costs I/we have incurred in preparing the proposal.

The proposal submitted herewith is a bona fide proposal intended to be competitive.
We have not fixed or adjusted the amount of the proposal by or under or in accordance with any collusive agreement or arrangement with any other person.

NAME OF PRINCIPAL INVESTIGATOR:	**Dr. Homberg Homberg**
SIGNATURE:	
DATE:	**October 11th 2016**