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Title of the project:

Positive Emotions Program for Schizophrenia (PEPS): a randomized controlled study on improving pleasure and motivation in schizophrenia

Cartoons by Sébastien Perroud, PET

1. Summary of the research plan (max. 1 page)

Background: The core features of schizophrenia include negative symptoms, which manifest themselves as absences or decreases in normal emotions and behaviors, and positive symptoms, which reflect excesses or distortions of normal functions. Drug-based treatments are highly effective on positive symptoms, such as hallucinations and delusions, but have limited efficacy on negative symptoms. Nonspecific psychosocial treatments have also shown few clinical effects on negative symptoms. Just as the psychosocial treatment of positive symptoms has improved by focusing more closely on delusion or hallucination, perhaps the psychosocial treatment of negative symptoms should also address specific targets. Recent literature has distinguished the negative symptoms associated with a diminished capacity to experience (apathy, anhedonia) from symptoms associated with a limited capacity for expression (emotional blunting, alogia). Anhedonia, which is defined as a reduction in the ability to experience pleasure, and apathy, which is related to a difficulty in anticipating the future, are good candidates for the development of a more specific psychosocial approach. Studies have shown that individuals with schizophrenia experience similar consummatory pleasure to controls, but less anticipatory pleasure. The combination of all these aspects led us to develop an intervention based on training the emotional and cognitive skills specifically needed to increase anticipatory pleasure in patients complaining of anhedonia or a lack of desire to engage in activities. A pilot study for the Positive Emotions Program for Schizophrenia (PEPS) demonstrated the intervention's feasibility. Preliminary results indicated that participation in PEPS was accompanied by a significant reduction of anhedonia, apathy, and depression in a group of patients diagnosed with schizophrenia or schizoaffective disorders. **Aim:** Using a randomized clinical trial (RCT), the proposed study will compare the efficacy of using PEPS to reduce symptoms of anhedonia and apathy against treatment as usual (TAU). **Methods:** Eighty participants diagnosed with a schizophrenia spectrum disorder will undergo one or the other intervention for eight weeks. The study's main hypothesis is that patients who have attended 8 one-hour sessions of PEPS will have lower total apathy-avolition and anhedonia-asociality scores on the Scale for the Assessment of Negative Symptoms (SANS), in comparison to the control group. The secondary hypotheses are that PEPS will increase patients' capacity to savor pleasure, anticipatory pleasure, and consummatory pleasure. The study will also monitor the sustainability of PEPS' potential benefits at a six-month follow-up. The necessary sample size was estimated using the results of the pilot study. Socio-demographic and clinical data will be collected using validated psychometric instruments, as will levels of psychotic symptoms, depression, and ability to savor, anticipate and consummate pleasure. Between-group differences in pre- and post-test values will be examined using an analysis of covariance (ANCOVA) for each outcome variable. Cohen's *d* effect sizes will be calculated: between subjects at post-test and follow-up and within-subjects between pre- and post-tests in correcting for dependence among means in order to directly compare the effect sizes from other studies. **Expected results and impact:** This RCT will test the clinical efficacy and potential sustainability of PEPS. Increasing the ability of individuals with schizophrenia to experience pleasure may have an impact on key elements of their recovery process, such as hope and motivation. The short duration of the training needed for professionals, and brief intervention itself, make PEPS quite easy to implement in a variety environments.

2. Research plan (the research plan must not exceed 20 pages and must not contain more than 80,000 characters, including spaces; minimal font of 10 and line spacing of 1.5; footer; figures, tables, formulas and references included)

2.1. Current state of research in the field

Negative symptoms have long been recognized as a central feature of the phenomenology of schizophrenia, dating back to early descriptions by Kraepelin and Bleuler (Foussias et al., 2014). They negatively affect patients' longitudinal social and occupational functional outcomes, as well their long-term recovery (Fervaha et al., 2014; Marder, 2013; Tsang et al., 2010; Ventura et al., 2013). Whereas positive symptoms (hallucinations, delusions) reflect an excess or distortion of normal functions, negative symptoms (flattened affect, alogia, apathy-avolition, anhedonia, inattentiveness) represent the absence or reduction of normal emotions and behaviors. Negative symptoms are classified as primary or secondary. Primary negative symptoms comprise the core features intrinsic to schizophrenia itself. Secondary negative symptoms are transient; they are attributable and temporally related to the effects of such factors as unrelieved positive symptoms, depression, the adverse effects of antipsychotic drugs (akinesia), or the social isolation imposed by the stigma of schizophrenia. Primary and secondary negative symptoms may be similar in clinical expression, despite their contrasting etiologies (Moller, 2007). Often, secondary negative symptoms diminish with the resolution of their causative factors. However the efficacy of drug-based treatments and psychological interventions on primary negative symptoms remains limited (Erhart et al., 2006; Fusar-Poli et al., 2014; Turkington and Morrison, 2012). Fusar-Poli et al. (2014), in their meta-analysis with 6,503 patients in the treatment arm and 5,815 patients in the placebo arm, showed that most treatments reduced negative symptoms at follow-up relative to placebo: second-generation antipsychotics, effect size −0.579 (−0.755 to −0.404); antidepressants, −0.349 (−0.551 to −0.146); combinations of pharmacological agents, −0.518 (−0.757 to −0.279); glutamatergic medications, −0.289 (−0.478 to −0.1); and psychological interventions, −0.396 (−0.563 to −0.229). However, none of the treatments used reached the threshold for clinically significant improvement. Current psychosocial treatments of negative symptoms include cognitive behavioral therapy (CBT), social skills training (SST), mindfulness-based interventions (MBI), cognitive remediation training (CRT), and combined treatments. Many of the combined treatments include family therapy and/or psychoeducation.

The next few paragraphs summaries the recent comprehensive literature review by Elis et al. (2013) to better understand the challenges of new program development.

Cognitive behavioral therapy – CBT. Overall, 13 of 21 randomized controlled trials (RCT) found that CBT was associated with an improvement in negative symptoms, either at post-treatment or follow-up (Elis et al., 2013). Most of the studies (5/8) that did not report improvements in negative symptoms included an active control group. A specific meta-analysis showed that the pooled effect-size for 34 studies of negative symptoms was -0.13 (95% CI, 70.25 to 70.01, p= 0.03). When controlling for randomization (sequence generation and allocation concealment), masked assessment, and attrition bias, the effect for negative symptoms was not significant. CBT interventions ranged from 2–18 months, with a mean of six months. In the review by Elis et al. (2013), only three of five studies investigating group CBT showed evidence of improvement (Bechdolf et al., 2004; Borras et al., 2009; Drury et al., 1996). Four trials (Bechdolf et al., 2004; Rector et al., 2003; Startup et al., 2004; Turkington et al., 2006; Turkington et al., 2002) found that CBT was more

effective than treatment as usual (TAU) 3–12 months after treatment, and one trial (Sensky et al., 2000; Turkington et al., 2008) found that CBT was more effective than an active treatment control five years after treatment.

Social skills training – SST. Although SST is not initially conceptualized as a treatment for negative symptoms, some studies have suggested that SST can be effective for improving negative symptoms in the short-term (Horan et al., 2009; Lecomte et al., 2008; Rus-Calafell et al., 2013; Xiang et al., 2006). One study using SST failed to demonstrate improvement of negative symptoms (Hayes et al., 1995). Two studies reported that the gains obtained had persisted at six-month follow-up (Rus-Calafell et al., 2013; Xiang et al., 2006), and one reported gains at three-month, but not at six-month follow-up (Dobson et al., 1995). These SST interventions ranged from nine weeks to 24 months, with a mean of 8.75 months. The advantage of SST is that it is usually conducted in group settings. A few studies have combined SST and CBT but found no improvements in negative symptoms as compared to TAU (Granholm et al., 2005), supportive therapy (Pinto et al., 1999), or waitlist groups (Daniels, 1998) .

Mindfulness based interventions – MBI. A meta-analysis involving 468 participants showed that these kinds of interventions were moderately effective in treating negative symptoms and could be a useful adjunct to pharmacotherapy; however, more research is necessary to identify the most effective elements of MBI (Khoury et al., 2013). Only half of the studies (7/13) were controlled with random assignment; the others were within-subject pre-post studies. Results showed that MBI are moderately effective in pre-post studies. When compared to a control group (waitlisted, TAU, or other treatments), effect sizes were small to moderate. The duration of the interventions ranged from 3–24 hours.

Cognitive remediation training – CRT. Studies using CRT alone, designed to train basic cognitive abilities such as memory, attention, or executive functions did not seem to have been effective in improving negative symptoms (d'Amato et al., 2011; Dickinson et al., 2010; Hodge et al., 2010; McGurk et al., 2009; Wykes et al., 2007). However combining CRT with SST may be useful for reducing negative symptoms, particularly social withdrawal, affective flattening, and motor retardation (Eack et al., 2009; Eack et al., 2013), or a global score of negative symptoms (Farreny et al., 2012). These interventions required 32–100 hours of training.

Combined intervention. According to Elis et al. (2013), only two studies have specifically compared the efficacy of combined treatments to the separate individual treatments, rather than comparing the combination to a TAU or waitlist condition (Hogarty et al., 1991; Hogarty et al., 1997). Both found that the combined treatment was associated with a greater improvement in negative symptoms. The majority of studies that included some type of family participation component demonstrated an improvement in negative symptoms. The other studies compared combination treatment conditions to a control condition (e.g., TAU, supportive therapy, another combined treatment, or a waitlist condition). It is thus impossible to interpret whether the combined treatment approach provided additional benefits above and beyond the benefits of the individual treatment packages. The two studies that looked at family therapy alone found an improvement in negative symptoms (Dyck et al., 2000; Girón et al., 2010). Most of the combined studies did not include follow-up assessments, and thus it remains unclear whether symptom improvements

persisted in the long-term. One three-year study (Hogarty et al., 1997) indicated that improvements in negative symptoms did not occur until the second and third year of therapy, while a second study (Petersen et al., 2005; Thorup et al., 2005) indicated improvements in negative symptoms at 12 and 24 months; this suggests that longer interventions are needed. This two-year, comprehensive program including assertive community treatment, social skills training, and multifamily therapy groups led to a significant reduction of positive and negative symptoms, less comorbid substance abuse, and significantly greater satisfaction with treatment. These comprehensive packages are promising but involve relatively long interventions and call for a broad range of therapeutic techniques. 'Negative symptoms' is a large and complex concept. Even if the variety of negative symptoms appears to be a homogenous group of symptoms, it is not yet clear whether their underlying neuropathology should be understood as a unified syndrome or as a group of distinct symptoms (Donohoe and Robertson, 2003; Winograd-Gurvich et al., 2006). The addition of psychoeducation was associated with an improvement in negative symptoms in only one of the three studies that added a psychoeducation element and measured negative symptoms (Buchkremer et al., 1997; Magliano et al., 2006; Rosenbaum et al., 2005, 2006). However, the specific impact of psychoeducation on negative symptoms was not directly tested.

This review indicates that there is a clear clinical need for developing treatments for negative symptoms. The lack of clinically meaningful efficacy of drug or psychological treatments is in line with clinicians' practical experiences (Erhart et al., 2006; Fusar-Poli et al., 2014). Family interventions to reduce negative symptoms appear promising. However, patients who have family members willing to be involved in treatment may merely represent a subgroup of people with schizophrenia. Furthermore, families which are more willing to participate to psychosocial interventions may provide patient's with greater support anyway and thus may not represent the broader population. Many patients with severe negative symptoms live in sheltered accommodation. A lot of studies have compared psychological interventions, but only two have studied the potential additional benefits of combining them (Hogarty et al., 1991; Hogarty et al., 1997). The treatments used in these studies (CBT, SST, MBI, or family therapy) required highly trained therapists. The great majority of these studies were not specifically designed to target negative symptoms, and most assessed negative symptoms overall, without looking for the specific effects of the control variable. Several interventions were provided over long durations, requiring a great investment in time by the patients. Except SST, very few interventions are provided as group therapy. Group interventions are particularly important since they are more commonly used in community psychiatry settings, where most patients receive treatment services.

2.2. Current state of your own research

Towards a symptoms approach to negative symptoms

Recent literature has distinguished the negative symptoms associated with a diminished capacity to experience (apathy, anhedonia) from those which are associated with a limited capacity for expression (emotional blunting, alogia) (Blanchard and Cohen, 2006; Foussias and Remington, 2010; Hartmann et al., 2015; Strauss et al., 2013). The apathy-anhedonia syndrome tends to be associated with a poorer prognosis than the symptoms related to diminished expression, suggesting that it is the more severe facet of the psychopathology (Strauss et al., 2013). This syndrome is

also related to the duration of the untreated psychosis, family history of schizophrenia, and the patient's work status in first-episode schizophrenia (Ergul and Ucok, 2015). The distinction between diminished experience and limited expression syndromes allows more specific approaches to these problems.

A symptom-specific strategy has been used in the development of specific therapeutic techniques for positive symptoms (Chadwick et al., 1996; Favrod et al., 2006) and led to the development of more effective interventions, such as the cognitive behavioral therapy (CBT) of delusions or hallucinations (Zimmermann et al., 2005). More recently, metacognitive training (MCT), which targets associated specific cognitive biases, has appeared to be effective in reducing positive symptoms (Favrod et al., 2014a; Kumar et al., 2014; Moritz et al., 2014). The symptoms approach has opened the way for the development of new interventions for specific negative symptoms, particularly for anhedonia. Anhedonia has been defined as a reduction in the ability to experience pleasure. Despite its clinical significance, research into anhedonia has produced a paradoxical set of findings, raising questions about its nature. On the one hand, using self-reported measures of trait social and physical anhedonia, individuals with schizophrenia typically report experiencing lower levels of pleasure in their daily lives than non-patients (Blanchard et al., 2001; Harrow et al., 2005; Herbener and Harrow, 2004; Herbener et al., 2005). On the other hand, individuals with schizophrenia have repeatedly reported experiencing levels of pleasant emotions similar to, or even stronger than, non-patient control subjects in laboratory studies using emotionally evocative stimuli (Gold et al., 2008; Kring, 1999; Kring and Earnst, 1999). Germans and Kring (Germans and Kring, 2000) resolved this inconsistency by suggesting that patients do not anticipate that pleasurable activities will indeed be pleasurable, even though they experience pleasant emotions when presented with pleasurable stimuli. This explanation is based on the distinction between appetitive/anticipatory pleasure (i.e., anticipating the potential pleasure of taking part in a future activity) and consummatory pleasure (i.e., the actual level of pleasure experienced directly from participating in an activity). Anticipatory pleasure is linked to motivational processes that promote goal-directed behaviors, while consummatory pleasure is associated with satiety. The Temporal Experience of Pleasure Scale (TEPS) is a trait measure of pleasure (Gard et al., 2006b) that distinguishes between 'momentary pleasure' and 'anticipation of future pleasant activities.' A TEPS score study, comparing subjects with schizophrenia to controls, indicated that patients did not differ from controls on the consummatory scale, however, they reported significantly less anticipatory pleasure than controls (Gard et al., 2007). These results were replicated by the French version of TEPS. Bringing out this new way of conceptualizing anhedonia in schizophrenia permits a redefinition and calibration of the symptom complex as a target for treatment. If persons with schizophrenia show a deficit in their ability to anticipate pleasure, rather than experience pleasure, then cognitive training might well help these individuals anticipate pleasure from foreseeable, future activities. Ideally, treatment would lead to a greater ability to anticipate pleasure, and this in turn would lead to a meaningful increase in spontaneous daily activities. These considerations led us to explore the potential for an intervention training patients who complained of anhedonia, or a lack of desire to engage in activities, in the cognitive skills needed to increase their anticipatory pleasure (Favrod et al., 2010). This first, exploratory pilot study included five participants with schizophrenia, presenting severe anhedonia, and stabilized on atypical antipsychotic medication. They received 10–25 hours of training in anticipatory pleasure. Results

showed that the patients improved on the anticipatory scale of TEPS. The patients' daily activities were also increased according to a time budget. These preliminary data were, of course, interpreted with caution, given the small study sample, but they seemed to show a promising path towards the development of new interventions to alleviate anhedonia in schizophrenia.

Recent research has also shown that more specific symptom or syndrome approaches better enabled the identification of specific psychological mechanisms. For example, the endorsement of beliefs regarding low expectations of success, and perceptions of limited resources, are robustly associated with negative symptoms of diminished experience (avolition, asociality, and anhedonia), but are not associated with negative symptoms of diminished expressivity (blunted affect, alogia). Similarly, defeatist performance beliefs are slightly related to diminished experience, but not at all related to diminished expression (Couture et al., 2011). An impaired ability to envision the future is associated with apathy (Raffard et al., 2013). These results suggest that within the syndrome of diminished capacity to experience, apathy and anhedonia may be the results of the same underlying process: that is, a diminished capacity to anticipate a particular experience or the achievement of a pleasurable goal (Foussias and Remington, 2010) or a motivational impairment (Strauss et al., 2014).

Further emotional deficits may be present in schizophrenia (Kring and Elis, 2013) and should be taken into account in the development of new interventions (Favrod et al., 2014c; Strauss, 2013). Strauss (2013) suggested maximizing positive emotional experiences by using techniques developed in the field of affective science (Bryant, 2007; Quoidbach et al., 2010) to increase the frequency and duration of positive emotional experiences. Five techniques have been found to specifically and reliably increase the frequency, intensity, and duration of positive emotions, including anticipating the enjoyment. The others were: behavioral display (expressing emotions via nonverbal behaviors); being 'in the moment' (directing controlled attention toward positive experiences when they occur—savoring); communicating and celebrating positive experiences with others; and recalling previously pleasurable events. Patients reported lower levels of pleasure in savoring past, present, and future events than did normal controls, and stated that they had low expectations of their self-efficacy (Cassar et al., 2013). Individuals with schizophrenia also manifested a lesser ability to maintain positive emotions (Horan et al., 2010; Kring et al., 2011; Ursu et al., 2011). Even though observable, outward signs of emotional expression were lessened in schizophrenia, studies indicated that sufferers continued to display very subtle facial muscle movements (as measured by electromyogram) similar to, and in accordance with, their responses (Kring and Moran, 2008). Finally, to the best of our knowledge, it appears that communicating and celebrating positive events with others has not been studied in schizophrenia patients. However, one study showed that impaired perspective-taking—a component of cognitive empathy—was associated with poor capacity and community functioning, even after taking into account the influences of neurocognitive deficits and psychopathology (Smith et al., 2012).

Positive Emotions Program for Schizophrenia (PEPS)

With this as a background, Jérôme Favrod and Alexandra Nguyen conceived an intervention they named the 'Positive Emotions Program for Schizophrenia' (PEPS), which aims to reduce anhedonia and apathy. The program teaches skills to help overcome defeatist thinking (Grant and Beck, 2009; Rector, 2004) and to increase the anticipation and maintenance of positive emotions (Favrod et al., 2014b; Kring and Elis, 2013). PEPS involves eight one-hour group sessions, administered using visual and audio materials as part of a PowerPoint presentation of slides projected onto a screen. Each session includes a number of the following steps. Part one begins with a welcome, followed by a five-minute relaxation-meditation exercise. In part two, the group leaders go over the homework task given during the previous session. Part three involves an exercise in challenging specific defeatist thoughts, which are presented using the program's two fictitious heroes—Jill and Jack. Jill, for example, expresses such defeatist thinking as "I can't relax; I'm useless." The participant's role is to challenge her belief, initially by assigning different reasons to why Jill has difficulty relaxing. They learn to find reasons which might be linked to the program's hero, but also to other people or to Jill's environment. They subsequently try to develop an alternative, more positive way of thinking. Subsequently, and according to the session's theme, participants learn and practice a new skill to improve their anticipation or maintenance of pleasure. The session ends with group leaders setting the homework task that the participants must accomplish for the next session.

The skills taught include savoring a pleasant experience, expressing emotions by increasing behavioral expression, making the most of, or capitalizing on, positive moments, and anticipating pleasant moments. Savoring an agreeable experience involves becoming aware of that pleasure or of the positive emotions the participant feels at a given moment (Bryant, 2007). For example, participants are asked to look at a picture of pleasant countryside or listen to soothing music, and hence become aware of the pleasurable experience of doing this and thus appreciate it. Increasing behavioral expression of emotions involves using facial expressions or gestures to accompany that positive emotion. The participants are asked to imitate pictures of actors expressing a positive emotion and to become aware of the sensations this produces. Making the most of positive moments entails communicating and celebrating positive events with others. For example, participants are invited to describe positive events to one another through role-play. Anticipating pleasant moments involves imagining the sensations produced by a positive future event. This strategy is meant to guide the participants through different positive feelings and emotions. It can engage their different senses, for example, by imagining they are eating a fruit, or by anticipating the emotion produced and the physical sensations experienced upon the completion of a pleasurable physical or social activity. A simple homework task is assigned to be done between each session. For example, this could be, choosing an image or an object that provokes a positive emotion or feeling in the participant, who must then bring it back and present it to the group. The pedagogical concept underpinning the program was built according to Kolb and Kolb's model (2008) of experiential learning. Each learning activity involves: 1) concrete experience, during which the participant completes a concrete task; 2) reflective observation, during which the participant reflects on his/her experience, his/her past—the participant communicates about the completion of the task; 3) abstract conceptualization, during which the participant interprets events—

theoretical links are created or introduced by a third party; and 4) active experimentation, during which the participant anticipates a new means of trying out the task, in light of the skills acquired in the preceding phase, and then executes them. The program uses a collaborative, egalitarian approach. Group facilitators participate in sessions just as the participants do, by doing the exercises, sharing their experiences, and carrying out the given tasks.

Patients participate in eight one-hour PEPS sessions at a rate of one per week. PEPS can be downloaded at : http://homepage.hispeed.ch/Jerome_Favrod/peps.htm.

PEPS Pilot Study

This pilot study was conducted between May and December 2014. Participants were recruited at three social and nursing homes in Lausanne, Rolle, and Marsens—towns in French-speaking Switzerland. The inclusion criteria were: 1) fulfilling the criteria of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), for a diagnosis of schizophrenia or a schizoaffective disorder; 2) presenting a score of at least 2 on the overall *Scale for the Assessment of Negative Symptoms* (SANS) anhedonia scale; 3) being aged between 18 and 65 years old; 4) being able to read and understand French; and 5) demonstrating capacity for consent according to the *San Diego Brief Assessment of Capacity to Consent (Jeste et al., 2007)*. This last tool measures a patient's understanding of an information sheet.

Participants were assessed using the SANS scale (Lecrubier and Boyer, 1987b), the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993), and the Savoring Belief Inventory (SBI) in pre- and post-tests as part of standardized interviews with a psychologist trained in their administration. The average time needed to complete the scales with one participant was one hour. The study was accepted by the Vaud Cantonal Ethics Commission on Human Research on 6 May 2014 (protocol 127/14).

Thirty-nine participants were recruited, two of whom subsequently refused to give their consent for the study. The final group was composed of 24 men and 13 women, with an average age of 41.84 years old (SD = 11.99). Thirty-one met the criteria for ICD-10 schizophrenia, and six met the criteria for a schizoaffective disorder. Their mean duration of illness was 19.05 years (SD = 12.85). Twenty-eight were single, eight were separated or divorced, and one was a widower. In terms of the educational level achieved: six had not finished mandatory schooling, 17 participants had finished their mandatory schooling, three had a secondary school diploma, eight had completed a professional apprenticeship, and three had either a professional school or university diploma. Three participants lived independently, two lived with their families, and thirty-two lived in sheltered housing. None of the participants had a job on the competitive labor market. Twenty-eight participants completed all eight sessions, two completed seven sessions, and one participant in each of the four cohorts only completed four sessions. Of the six participants who dropped out, one refused to participate after the first assessment, one moved away, and four left the program before it finished. Two of these refused to continue the program, without giving an explanation as per the informed consent form. However, the four others provided reasons for giving up which were unconnected with the program (external stressors). Participants who dropped out did not differ from those who completed the program. In post-tests, the participants had significantly

reduced the average total scores for the SANS avolition-apathy (t=3.84; df(30); p=.001) and anhedonia-asociality (t=3.81; df(30); p=.001) scales. They exhibited Cohen's *d* effect sizes of 0.50 for the anhedonia-asociality scale and 0.57 for the avolition-apathy scale, resulting in a moderate overall effect size. The average total score for the CDSS also showed a significant improvement in the post-test (t=4.61; df(30); p=.000), with a Cohen's *d* effect size of 0.91. Finally, the average total score for the SANS and the average total score for the Savoring Belief Inventory both showed small effect sizes, however, they were not statistically significant because the Bonferroni correction needed (p <.01) for multiple comparisons.

This initial study demonstrated that the Positive Emotions Program for Schizophrenia was a feasible treatment method. The preliminary results, presented here, indicate that completing PEPS was accompanied by a reduction in anhedonia, apathy, and depression in a group of participants diagnosed with schizophrenia or schizoaffective disorders. These results are encouraging and suggest the need for an RCT. Furthermore, the scientific results were corroborated by the patients' enthusiasm and diligent participation, something that is not customary in such a population. This pilot study has some limitations. Firstly, since there was no control group, the psychologist who assessed the participants was not blind. The absence of a control group does not adjust for the personal attention given to the participants. A novelty effect is possible according to the enthusiasm of the participants who advertise to invite other patients to come to the program. The results of this pilot study are currently under review by Schizophrenia Research (Favrod et al., submitted).

2.3. Detailed research plan

The pilot study described above confirms the feasibility of PEPS. The reduction of apathy and anhedonia accompanying PEPS makes it an interesting candidate for further investigation. The goal of the study proposed herein is to establish whether PEPS is clinically effective by using a randomized, controlled, and assessor-blind trial. A combination of PEPS plus treatment as usual (PEPS+TAU) will be compared to TAU alone. Eighty participants diagnosed with a schizophrenia spectrum disorder will undergo either intervention for eight weeks. Testing will evaluate individuals' current psychopathology and ability to savor pleasure, and will be performed at the time of inclusion, at the end of the eight-week intervention, and eight weeks after that.

Hypotheses

This trial's main hypothesis is that eight one-hour sessions of PEPS will lead to a reduction of the total apathy-avolition and anhedonia-asociality scores on the SANS compared to the control group. Our secondary hypotheses are that PEPS will increase the capacity to savor pleasure, anticipatory pleasure, and consummatory pleasure, as well as reduce depression. The study will also monitor the sustainability of the potential benefits at a six-month follow-up.

Sample size and power considerations

The optimal sample size has been estimated using the results of the pilot study. For the sample size calculation, α was set at .025 with a Boneferroni correction because the trial will test the programs' efficacy on the apathy-avolition and anhedonia-asociality scales of the SANS. A β was set conservatively at .95 in order to avoid a false negative error. From

the results of the pilot study, the Cohen's *d* for our two variables is between .50 and .57, or the partial eta - η2 respectively of .326 and .330. As the participants in the pilot study were not masked from the assessor and because trials in which raters are aware of group allocation tend to have an inflated effect size (Jauhar et al., 2014), we decided to halve this effect size to .164. Using an a priori computation for an ANCOVA, the proposed trial requires a total sample size of 80 participants for the two arms. With a drop-out rate of 16%, we estimate that we should include 94 patients and screen about 120 potential participants.

Recruitment and screening

Patients will be recruited among the population of out-patients treated at the HorizonSud Foundation in the canton of Fribourg and at the Social psychiatry section of the Community Psychiatry Service, Department of Psychiatry, University Hospital Centre of Lausanne. Horizonsud is a social foundation offering sheltered accommodation and work to psychiatric patients from the south of the canton of Fribourg (the Gruyère, Glâne and Veveyse areas). The foundation takes care of 250 patients. The Social psychiatry section treats patients aged from 18 to 65. The 400 or so patients likely to fulfil the diagnostic criteria for recruitment to the proposed study are treated in the rehabilitation unit and work closely with the canton of Vaud's sheltered accommodation services. Both teams are trained and used to dealing with ethical issues, randomization, masking participants' conditions from raters, and other research procedures. Potential participants will be identified using systematic screening alongside the patients' case managers and medical doctors. An appointment will be organized between the patient, case manager, and research coordinator in order to explain the study, provide information, and obtain informed consent. This strategy was applied successfully during the pilot study and enabled the recruitment of 37 subjects over a nine-month period.

Eligibility for study inclusion

Inclusion criteria for patients are as follows: 1) a psychotic disorder according to ICD 10 (F20 or F25), diagnoses having been established by experienced clinicians; 2) presenting a score of at least 2 on the overall SANS anhedonia scale; 3) age between 18 and 65 years old; 4) French-speaking; 5) sufficient clinical stability to be able to provide informed consent. Exclusion criteria: 1) evidence of organic brain disease, clinically significant concurrent medical illness, or learning disability; 2) no understanding of the study protocol as assessed with a decisional capacity instrument (Jeste et al., 2007).

Ethical considerations - Information and consent

After initial screening, eligible patients will be asked to participate in the study. Each patient included will be informed about: the aims of the study; the extent and nature of their participation, including randomization; the nature of the control and experimental interventions; the intake assessment; and six-month follow-up evaluation. The patients included will also be informed about data confidentiality and their right to withdraw from the study at any time. Once the participant has given his/her consent, their understanding of the study protocol will be verified using the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC)—a decisional capacity instrument (Jeste et al.,

2007). Our research group is familiar with this instrument, and in cases of failure to clearly understand the study, patients will not be included. Finally, each patient will sign the informed consent form (Favrod et al., 2014a). The study protocol has been submitted to the Vaud Cantonal Ethics Commission on Human Research. The protocol for the pilot study was accepted by the same Commission on 6 May 2014 (protocol 127/14).

Randomization

A research manager who is not involved in the clinical part of the trial will randomize participants by blocks of 8, 10, or 12 patients. The size of the blocks will depend on the speed at which recruitment occurs in order to minimize the time between the baseline assessment and allocation in the treatment arms.

Independence of raters

The independence of the raters will be controlled for as follows. At baseline, participants will be randomized following their initial evaluation. Participants will be informed when they give their consent, and again when their appointments for post-test and follow-up meetings are scheduled, that it is extremely important they do not to reveal their treatment group allocation to the raters. The raters will not work in the places where intervention takes place and will not be present during group sessions in order to avoid encounters with participants. Raters will not participate in clinical meetings or group facilitator supervision. Meetings with the raters will be organized by the research coordinator by site (HorizonSud and the Section of social psychiatry). To check whether masking of the participants'allocation from the raters has been successful, raters will answer a brief questionnaire at the end of post-test and follow-up assessment periods. This questionnaire will measure their guesses about the participants' treatment allocations and identify potential cues which might unmask them. Our research group is familiar with this procedure (Favrod et al., 2014a).

Treatment as usual (TAU)

TAU was chosen as a control condition for a number of reasons. First, in the Lausanne or Gruyère areas, TAU is multi-facetted and thus assures the ethicality of our procedure. TAU consists of psychiatric management by a clinical team composed of at least one psychiatrist and a social worker and/or a psychiatric nurse with additional access to community treatment or hospital admission. Treatment involves antipsychotic medication, regular office-based or community contact with the clinical team for treatment monitoring, and socialization groups, therapy, and psychoeducational groups. No attempts have been made to standardize this treatment as TAU is tailored to the patient's specific needs.

Positive Emotions Program for Schizophrenia (PEPS)

The initial version of PEPS, as described in the pilot study section of this application, will also be used for the RCT. It is currently being improved to make its format more attractive, including using original illustrations. In particular, the two fictitious heroes—Jill and Jack—will now be represented using cartoons (see title page).

Participants will receive eight one-hour sessions of PEPS at a rate of one per week.

Session List:

- Session 1: defeatist thinking
- Session 2: savoring pleasant moments (I)
- Session 3: accentuating the behavioral expression of emotions
- Session 4: making the most of pleasant moments by sharing them with others
- Session 5: savoring pleasant moments (II)
- Session 6: anticipating pleasant moments (I)
- Session 7: anticipating pleasant moments (II)
- Session 8: review of all skills.

Participants will conduct the review exercises themselves, during the last session. The trainers themselves will receive six hours of training and two one-hour supervisions during the RCT, as in the pilot study.

Assessment tools

As part of their standardized interviews at the pre- and post-tests, participants will be assessed using the following form by a psychologist trained in its administration:

- Collection of socio-demographic and clinical data: age, sex, psychiatric diagnosis, duration of illness, living arrangements (e.g., nursing home, with family), treatment, etc. These data will be collected at base-line assessment and reassessed for living arrangements and treatment at six-month follow-up.

The following scales will be administrated at baseline assessment, post-test, and six-month follow-up by a psychologist trained in their administration:

- *The Scale for the Assessment of Negative Symptoms* (SANS) (Lecrubier and Boyer, 1987b). This scale measures schizophrenia's deficit symptoms within the framework of schizophrenic disorders. It comprises 25 items, scored from 0 to 5. A definition of each item, including examples, facilitates a better understanding of the scale's content. The rating system is ordinal, from 0 (absent) to 5 (severe). The 25 items are grouped into five components: 1) withdrawal or emotional poverty; 2) alogia (lack of speech); 3) avolition and apathy (lack of energy, lack of initiative); 4) anhedonia and social withdrawal (loss of interests); 5) attention.. The scale was translated into French with acceptable validity (Dollfus et al., 1995; Lecrubier and Boyer, 1987a). The total scores for the avolition-apathy and anhedonia-social withdrawal components will be used as the main outcome variables.

The Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1993) includes nine items: depression, hopelessness, self-depreciation, guilty ideas of reference, pathological guilt, morning depression, early wakening, suicide, and observed depression. This scale has been validated in French (Reine et al., 2000). The rater will be kept blind to the participation arm's random assignation.

The following self-report scales will be administrated at baseline assessment, post-test, and six-month follow-up by a psychologist trained in their administration:

- *The Savoring Belief Inventory (SBI)* is a self-reported scale for measuring beliefs about one's capacity for savoring things. The scale has 24 items, including a positive scale (12 items) and a negative scale (12 items). The scale has good validity and a high test-re-test reliability (Bryant, 2003). It measures a person's thinking regarding their capacity to savor positive experiences, in terms of past experiences, current experiences, and future anticipation. The total SBI score will be used as a secondary outcome variable.
- *The Temporal Experience of Pleasure Scale (TEPS)* contains 18 items included in two sub-scales: anticipatory pleasure (10 items) and consummatory pleasure (8 items) (Gard et al., 2006a). Items targeting anticipatory pleasure reflect the pleasure felt when anticipating a positive or pleasant stimulus. Items measuring consummatory pleasure refer to the direct pleasure experienced upon exposure to a stimulus. Items can be general or specific. The response to items falls on a six-point Likert scale from 1 (very false for me) to 6 (very true for me). This scale has been validated in French (Favrod et al., 2009). The total TEPS score will be used as a secondary outcome variable
- *The Anticipatory and Consummatory Interpersonal Pleasure Scale (ACIPS)* (Gooding and Pflum, 2014a, b) is designed to assess one's ability to experience pleasure in the interpersonal domain. It is a seventeen-item self-reported measure that consists of seven anticipatory and 10 consummatory items. The ACIPS is scored on a six-point Likert scale, ranging from 1 (very false for me) to 6 (very true for me). The format is therefore quite similar to that of TEPS. The difference between the two scales lies mainly in terms of the items' content. The total ACIPS score will be used as a secondary outcome variable.

The average time needed to complete the scales and the clinical interview with the participants is one hour.

The last scale will be completed by the case-manager of the participant at baseline assessment and six-month follow-up.

- *The Social Functioning Scale (SFS)* (Birchwood et al., 1990) is constructed to assess those areas of functioning that are crucial to the community maintenance of individuals with schizophrenia. This is a reliable, valid, sensitive and responsive to change instrument.

Statistical analyses

Between-group differences in post- and pre-test values will be examined using an analysis of covariance (ANCOVA) for each outcome variable. Differences between pre-test and post-test, as well as pre-test and follow-up scores, will be treated as dependent variables; treatment condition will be treated as a fixed factor; and pre-treatment scores will be treated as covariates. Between-subjects Cohen's *d* effect sizes will be calculated at post-test and follow-up. For within-subjects Cohen's *d* will be calculated between pre- and post-test, and pre-test and follow-up, in correcting for dependence among means. This will enable direct comparisons with the effect sizes from other studies.

The trial will be registered on an approved public site.

2.4. Schedule and milestones

The study will start on October 1, 2015 and finish on September 30, 2018. The schedule below illustrates the different steps of the protocol.

Schedule

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Recruitment and assessment																																				
Screen and enrol participants																																				
Baseline assessment																																				
Interventions																																				
PEPS																																				
Post-test																																				
Post-test assessment																																				
Follow-up																																				
Follow-up assessments																																				
Data analysis																																				
Data entry																																				
Continuing analysis																																				
Final analysis																																				
Knowledge sharing																																				
Congress presentations																																				
Preparation of publications																																				

2.5. Importance and impact

This RCT will establish the clinical efficacy and test sustainability of PEPS. Compared to previous studies, PEPS aims to improve a specific diminished experience syndrome (apathy, anhedonia) which tends to be associated with a poorer prognosis than the symptoms related to diminished expression, suggesting that it is the more severe facet of the psychopathology (Strauss et al., 2013). This syndrome is also related to the duration of the untreated psychosis, family history of schizophrenia, and the patient's work status during first-episode schizophrenia (Ergul and Ucok, 2015). PEPS is a relatively brief intervention, involving eight one-hour group sessions, and led by trainers who only require six hours of training and two one-hour supervision sessions. This is of particular importance since patients with severe negative symptoms are monitored mainly by nurses and social workers in sheltered accommodation and workshops. The short duration of training required by the health and social professionals, and the short duration of the intervention for participants, however, remain quite valid and relevant. Firstly, budgets for continuous education are limited, and secondly, patients with severe negative symptoms will find it easier to participate in a short intervention than in a demanding, extended one. Increasing the ability of patients with schizophrenia to experience pleasure and to anticipate

future pleasure may have an impact on key elements in their recovery process, such as hope and motivation (Bonsack and Favrod, 2013; Bonsack et al., 2013; Favrod et al., 2014c; Favrod and Scheder, 2004).

The fact that PEPS has been built using an experiential learning model, in collaboration with a training engineer (Alexandra Nguyen), is quite new in psychological intervention, and may well explain a part of the success obtained by the pilot study. The program's structure promotes a collaborative, egalitarian approach. Group facilitators participate in sessions just like the participants, by doing the exercises, sharing their experiences, and carrying out the assigned homework tasks. This facet was greatly appreciated by the participants.

Local collaborations

The project is supported by the French-speaking Network of Peer Practitioners in Mental Health. Peer practitioners will be involved as PEPS facilitators.

A collaboration with Prof. Kim Q. Do, director of the Center for Psychiatric Neuroscience (Department of Psychiatry, Lausanne University Hospital) and head of the Unit for Research in Schizophrenia (URS) will contribute to the project by carrying out anhedonia-related EEG assessment before and after the PEPS clinical trial and explore blood biomarker of depression changes. If the present project is accepted an application for an EEG pilot study on anticipation, decision making and risk taking will be submitted in collaboration with the Haute Ecole de Gestion de Fribourg (HEG- FR - Prof. Philippe Régnier) and the Center for Psychiatric Neurosciences to the strategic funds of the University of Applied Sciences and Art of Western Switzerland for an inter-field project (health-management). The procedure could be adapted for a neuroeconomics study and to detect potential EEG change in PEPS' participants.

International collaborations

The following collaborations have already been set in place.

Diane C. Gooding, Professor of Psychology & Psychiatry at the Major University of Wisconsin-Madison, on the French validation of the Anticipatory and Consummatory Interpersonal Pleasure Scale. We share an interest in the assessment of the interface between affective and cognitive processing in schizophrenia and related disorders.

Pierre-Michel Llorca, Professor of Psychiatry at the University of Clermont-Ferrand, coordinator of the French network of Schizophrenia Expert Centers developed by the Foundation Fondamental, will collaborate on field tests for PEPS in France. Several member of his team have already been trained as group facilitators.

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