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ORIGINAL INVESTIGATION

Precision-medicine findings from the FACE-SZ cohort to develop motivation-enhancing programs in real-world schizophrenia

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ABSTRACT

Background: In people with schizophrenia, major areas of everyday life are impaired, including independent living, productive activities, social relationships and overall quality of life. Enhanced understanding of factors that hinder real-life functioning is vital for treatments to translate into more positive outcomes.

Aim: The goal of the present study was to identify factors associated with motivation deficits in real-life schizophrenia, and to assess its contribution to impaired functioning and quality of life.

Methods: Based on previous literature and clinical experience, several factors were selected and grouped into factors potentially explaining motivation deficits. Some of these variables were never investigated before in relationship with motivation deficits.

Results: In 561 patients with schizophrenia of the national FACE-SZ cohort living in the community, 235 (41.9%) reported severe motivation deficits. These deficits were found to be significantly associated with impaired socially useful activities, psychological and physical quality of life (in almost all domains), alcohol use disorder (aOR = 2.141, $p = 0.021$), severe nicotine dependence (aOR = 2.906, $p < 0.001$) independently of age and sex. No significant association was found for body mass index, metabolic syndrome or physical activity level. In the second model, we identified the following modifiable factors associated with motivation deficits: history of suicide attempt (aOR = 2.297, $p = 0.001$), positive symptoms (aOR = 1.052, $p = 0.006$), current major depressive episode (aOR = 2.627, $p < 0.001$), sleep disorders (aOR = 1.474, $p = 0.024$) and lower medication adherence (aOR = 0.836, $p = 0.001$) independently of gender, current alcohol use disorder, second-generation antipsychotics and akathisia. No significant association was found for negative symptoms, childhood trauma and inflammation. These results were maintained after removing patients with schizoaffective disorders or those with major depressive disorder.

Interpretation: Motivation deficits are frequent and remain persistent unmet need in real-world schizophrenia that should be addressed in future guidelines. Based on our results, literature and clinical experience, we recommend to address in priority major depression, sleep, suicide, positive symptoms (when present and as early as possible) and medication adherence to improve motivation deficits of schizophrenia.

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1. Introduction

Motivation deficits have been observed in schizophrenia from the first clinical descriptions of Bleuler ('having no urge to do anything either on their own initiative or at the bidding of another') and Kraepelin ('loss of mastery on volition') (Foussias and Remington 2010). Motivation deficits are currently gathered under the name of 'avolition' and defined in the DSM-5 as 'a decrease in motivated self-initiated purposeful activities' (American Psychiatric Association. 2013). Motivation includes directional (approach or avoidance) and energetic aspects (vigor and persistence in pursuing an outcome) (Bromberg-Martin et al. 2010; Salamone et al. 2016). There is consensus that motivation deficits are central to schizophrenia physiopathology from the early prodromal phase to the chronic phase of the illness (Gupta et al. 2021; Strauss et al. 2021) and that these deficits are different from those seen in mood disorders (Yang et al. 2021). Motivation deficits were considered as the most central of the five negative symptoms domain (the others being alogia, blunted affect, social withdrawal, and anhedonia) in the 2005 NIMH Consensus Conference (Kirkpatrick et al. 2006). Their central role has been confirmed in a recent symptoms network analysis (Strauss et al. 2021). It is now well established that they strongly impact the functioning and quality of life of people with schizophrenia (Fulford et al. 2018; Galderisi et al. 2018; Mucci et al. 2021; Uchino et al. 2021). They may also limit the success of interventions targeting risky health behaviour including losing weight (McGinty et al. 2016; Weye et al. 2021), increasing physical activity level (Vancampfort et al. 2015; Stubbs et al. 2017) and addictions cessation (Cather et al. 2017).

Among aetiological factors explaining motivation deficits in schizophrenia, a long list of potential culprits was missing from previous works. First, it is now consensual that the simultaneous evaluation of negative and depressive symptoms is important to clarify the relative contribution of these two psychopathological domains to real-life functioning (Galderisi et al. 2014). A recent meta-analysis has found motivation deficits at the crossroad of negative and depressive syndromes (Krynicki et al. 2018). Major depression has been identified in one third of the schizophrenia patients and remains underdiagnosed and poorly treated (Fond et al. 2018; Etchecopar-Etchart et al. 2021). Second, sleep disorders are identified in more than an half of schizophrenia patients and may also favour motivation deficits (Meyer et al. 2020; Sunhary de Verville et al. 2021). Third, chronic inflammation has been identified in two thirds of patients with schizophrenia (Fond et al. 2021). This inflammation may decrease motivation via the effects of inflammatory cytokines on the basal ganglia (Goldsmith and Rapaport 2020; Perry et al. 2021). Fourth, metabolic syndrome has been associated with cognitive deficits in schizophrenia and may therefore play a role in motivation deficits (Hagi et al. 2021). Fifth, addictions have complex relationships with motivation. Tobacco and cannabis smoking and alcohol misuse are frequent in schizophrenia and may have a bilateral relationship with motivation deficits (Bahorik et al. 2017; Laksmidewi and Soejitno 2021; Schermitzler et al. 2021). Sixth, some antipsychotic treatments induce secondary negative symptoms including motivation deficits (Artaloytia et al. 2006; Mas et al. 2013; Kirkpatrick 2014; Fervaha et al. 2015). Seventh, childhood trauma may induce long-term motivation deficits (Kasparek et al. 2020).

In summary, the importance of motivation deficits in the functioning and quality of life of schizophrenia is now established, but its impact on risky health behaviours and the potential aetiological factors has not been determined in a comprehensive real-world sample.

Our aim was therefore to determine the impact of motivation deficits on risky health behaviour in addition to functioning and quality of life, and to determine the factors associated with motivation deficits in real-world schizophrenia. Our hypothesis was that motivation deficits were associated with increased overweight/obesity and/or metabolic syndrome, decreased physical activity level, more frequent addictive behaviour in addition to impaired functioning and quality of life. Among potential aetiological factors, we hypothesised that a positive association would be found between motivation deficits and depression, sleep disorders, antipsychotics side effects, childhood trauma and inflammation.

2. Population and methods

2.1. Study population

The FACE-SZ (FondaMental Academic Centres of Expertise for Schizophrenia) cohort is a national cohort created in 2010. The participants were consecutively recruited at a national level in 10 Schizophrenia Expert Centres (Bordeaux, Clermont-Ferrand, Colombes,

Créteil, Grenoble, Lyon, Marseille, Montpellier, Strasbourg, Versailles) (www.fondation-fondamental.org) (Schürhoff et al. 2018; Fond et al. 2020).

2.1.1. Inclusion criteria

The participants included in this cohort are clinically stabilised patients (defined by no hospitalisation and no treatment changes during the 8 weeks before evaluation) with a DSM-IV-TR diagnosis of schizophrenia (F20*) or schizoaffective disorder (F25*). Diagnosis was confirmed at inclusion by two trained psychiatrists of the Schizophrenia Expert Centres network. Diagnoses interviews were carried out by two independent psychiatrists according to the Structured Clinical Interview for Mental Disorders (SCID 1.0) (First MB, et al 2002) module B to H (Psychotic and associated symptoms, psychotic disorders, mood disorders, substance use disorders, anxiety disorders, somatoform disorders and eating disorders).

2.1.2. Exclusion criteria

All patients with other diagnoses than schizophrenia (except for comorbid major depression, anxiety disorder, eating disorder and addictions) and those not speaking French were excluded.

2.2. Collected data

All participants included in the FACE-SZ cohort receive a one-day long standardised battery of clinical assessments. The present participants received the 2015-updated battery. The details of psychometric properties and the rationale for the choice of the scales are described in a synthesis article (Schürhoff et al. 2015).

2.2.1. Motivation deficits definition and measurement

No specific scale has been developed so far to assess goal-directed motivation in schizophrenia patients, and motivation is not explored in the most frequently psychotic symptom scale for schizophrenia, the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay et al. 1987). We have therefore chosen the dimension of motivation evaluated in the lifestyle self-reported questionnaire battery, the Pittsburgh Sleep Questionnaire Index (Buysse et al. 1989). In this questionnaire, participants were asked the following question: 'In the past 30 days, how difficult was it for you to be sufficiently motivated to carry out your activities?'. They had four modalities: Not difficult at all – Somewhat difficult – Slightly difficult – Very difficult. The participants answering 'very difficult' were classified in the 'severe motivation deficits' group, the others in the control group.

2.2.2. Variables potentially explained by severe motivation deficits

The first set of variables included variables that were considered as potentially impacted by motivation, despite the cross-sectional design of the study. The purpose was therefore to determine if motivation may explain these variables.

2.2.2.1. Functioning. We explored daily functioning with the Global Assessment of Functioning scale (GAF) (Startup et al. 2002) and the Professional and Social Performance scale (PSP) (Morosini et al. 2000) (four subscores: socially useful activities, personal and social relationships, self-care and disturbing and aggressive behaviours).

2.2.2.2. Quality of life. Quality of life was assessed using the Schizophrenia – Quality of Life – 18 items (SQoL-18) questionnaire (eight dimensions: Self-Esteem, Sentimental Life, Familial relationships, Friendships, Autonomy, Psychological Well-being, Physical Well-being, Resilience, and a total Index score) (Auquier et al. 2003; Boyer et al. 2010) and EuroQol-5 Dimensions (EuroQol-5) questionnaire (with 6 subscores: mobility, autonomy, mobility, physical pain, anxiety/depression and self-reported global health status) (Mulhern et al. 2014).

Outcomes associated with health risky behaviour. We included body mass index, metabolic syndrome, physical activity, tobacco smoking, severe nicotine dependence (defined by a Fagerström questionnaire score $\geq$7) (Heatherton et al. 1991), and alcohol and cannabis use disorders and clinical global impression score (Haro et al. 2003) in this section. Physical activity level was assessed with the Global Physical Activity Questionnaire (Rivière et al. 2018).

2.2.3. Variables potentially explaining severe motivation deficits

2.2.3.1. Sociodemographic and early life variables. The present study has a cross-sectional design and no causal relationship can be inferred. However, retrospective/early life data was collected, including education level (a continuous variable, number of years of scholarship from primary school), childhood trauma questionnaire, age at schizophrenia onset, age at first antipsychotic treatment, age at first thymic episode, lifetime number of thymic episodes and lifetime history of suicide attempt. This data was reported by the

patient, her/his relatives (when present) and from the medical records sent by the treating psychiatrist to limit memorisation bias.

2.2.3.2. Current symptomatology. As psychiatric symptoms may influence motivation, psychotic symptomatology (PANSS total score and positive and negative factors) (continuous), current depressive episode (Calgary Depression rating Scale for Schizophrenia score $\geq$ 6) (Addington et al. 1993) (binary), current manic episode (Young Mania Rating Scale score $\geq$12) (binary), current sleep disorder (Pittsburgh Sleep Questionnaire Index sleep disorder subscore (Buysse et al. 1989) (binary), insight into illness (Birchwood total score and subscale scores: insight into illness, insight into symptoms and insight into the need for treatment) (continuous), current eating disorder defined with the Structured Clinical Interview for Mental Disorders (SCID 1.0) (First et al. 2002)) (binary).

2.2.3.3. Substance consumption and physical health. Alcohol and cannabis use disorders were defined with the Structured Clinical Interview for Mental Disorders (SCID 1.0) (First et al. 2002)) (binary), tobacco smoking status (binary) and coffee consumption (binary) were self-reported and the presence of at least one physical chronic disease (binary) was determined with the medical records yielded by the patients, her/his relatives and her/his treating physicians. Metabolic syndrome definition was detailed in a previous paper (Godin et al. 2015) in accordance with the World Health Organisation recommendations. Inflammation was proxied by the high sensitivity C-reactive protein (hs-CRP) blood level that was measured with an assay using nephelometry (Dade Behring). Hs-CRP blood level has been described a good proxy of central inflammation (Felger et al. 2018).

2.2.3.4. Treatments and treatment side effects. We included treatment variables (second generation antipsychotics, anticholinergic drugs, clozapine treatment, antidepressants, mood stabilisers, benzodiazepine (binary variables)). The antipsychotic treatments were classified according to their Anatomical-Therapeutic-Clinical ATC class. First-generation antipsychotics (FGA) were defined by ATC class N05AA to AC (phenothiazines), NO5AD (butyrophenones), NO5AF (thioxanthenes). Second-generation antipsychotics (SGA) were defined by ATC class N05AH (diazepines, oxazepines, thiazepines and oxepines) and NO5AL (benzamides) (Misdrahi et al. 2019). Treatment side-effects were assessed with the continuous scores of validated scales (extrapyramidal symptoms with the Simpson&Angus Scale (Simpson and Angus 1970), akathisia with the Barnes Akathisia Scale (BAS) (Barnes 1989), sexual dysfunctions with the self-reported Sexual Functioning Questionnaire (SFQ) (Smith et al. 2002)). Medication adherence was assessed with the Medication Adherence Rating Scale (MARS) (continuous) (Fond et al. 2017).

2.3. Statistical analysis

All variables were presented using measures of means and dispersion (standard deviation) for continuous data and frequency distribution for categorical variables. The data was examined for normal distribution with the Shapiro–Wilk test and for homogeneity of variance with the Levene test. Comparisons between patients with severe motivation deficits and those without using the chi-square test for categorical variables. Continuous variables were analysed with Student t-tests for normally distributed data and in case of normality violation, additional Mann-Whitney tests were performed to confirm the result. As detailed in the rationale, the present study was hypothesis-driven, no correction for multiple testing has been therefore carried out (Bender and Lange 2001).

The following set of data was included in the univariate analyses of the model 1 (Table 1) aiming at exploring which variables could be explained by severe motivation deficits: Global Assessment of Functioning scale score, Professional and Social Performance scale total score and subscores, SQoL-18 total Index score and eight dimensions scores (Self-Esteem, Sentimental Life, Familial relationships, Friendships, Autonomy, Psychological Well-being, Physical Well-being, Resilience), EQ5D total score and its 6 subscores, body mass index, metabolic syndrome, Global Physical Activity Questionnaire score, current tobacco smoking and severe nicotine dependence, current alcohol and cannabis use disorders, Clinical Global Impression score. In multivariate analyses, one model was carried out for each variable associated with severe motivation deficits with a p value $<$0.20 in univariate analyses (Global Assessment of Functioning scale score, Professional and Social Performance scale total score and subscores, SQoL-18 and EQ5D total scores and subscores, Global Physical Activity Questionnaire score, severe nicotine dependence, current alcohol disorder. Age and sex were forced in all models.

The following set of data was included in the univariate analyses of the model 2 (Table 2) aiming at

explaining severe motivation deficits (motivation was considered here as dependent variable): age, sex, education level, childhood trauma questionnaire score, age at schizophrenia onset, age at first antipsychotic treatment, age at first thymic episode, lifetime number of thymic episodes, lifetime history of suicide attempt, PANSS positive and negative factors, current depressive episode, current manic episode, insight into illness (Birchwood total score and subscale scores: insight into illness, insight into symptoms and insight into the need for treatment), current eating, alcohol, cannabis use disorders, tobacco smoking status, coffee consumption, body mass index, metabolic syndrome, hs-CRP blood level, second generation antipsychotics, anticholinergic drugs, clozapine treatment, antidepressants, mood stabilisers, benzodiazepine, extrapyramidal symptoms Simpson&Angus scale score, Barnes Akathisia Scale score, Sexual Functioning Questionnaire score, medication Adherence Rating Scale score. Severe nicotine dependence was not included as this variable is reported for smokers only.The variables associated with severe motivation deficits with a p value <0.20 in the univariate analyses were included in the multivariate model (age, lifetime history of suicide attempt, PANSS positive factor, current depressive episode, Birchwood total score, current alcohol disorder, second generation antipsychotics, current sleep disorder, Barnes Akathisia Scale score, Medication Adherence Rating Scale score). Sex was forced. Metabolic syndrome, alcohol, cannabis and tobacco were therefore included in both model 1 and model 2 (as we assumed a bilateral association based on literature review).

To understand more precisely the symptoms associated with motivation deficits, the associations between motivation deficits and each of the PANSS and CDSS symptoms were analysed (univariate analysis) (supplementary Table 1). Two subgroup analyses were carried out to understand the role of mood disorders: one after removing patients with schizoaffective disorders and one after removing patients with major depressive disorder.

2.4. Ethical considerations

The study was carried out in accordance with ethical principles for medical research involving humans (WMA, Declaration of Helsinki) and the French Jardé law. The assessment protocol was approved by the relevant ethical review board (CPP-Ile de France IX, 18th January 2010). All data was collected anonymously. As this study include data coming from regular care assessments, a non-opposition form was signed by all participants.

3. Results

Overall, 561 patients (416 (74.2%) men, 138 (24.6%) with schizo-affective disorders, 120 (21.4%) with major depressive disorder) were included in the FACE-SZ cohort between 1st January 2015 and 31th December 2019. Overall, 235 (41.9%) were included in the 'severe motivation deficits' group.

3.1. Variables potentially explaining severe motivation deficits (*Table 1*)

In multivariate analyses, individuals with severe motivation deficits were found to be older (adjusted odds ratio (aOR) 1.031, $p = 0.009$), to have more frequently history of suicide attempt (aOR = 2.297, $p = 0.001$), to have slightly higher positive symptoms (aOR = 1.052, $p = 0.006$), and insight into illness (aOR = 1.104, $p = 0.013$), to be more frequently diagnosed with current major depressive episode (aOR = 2.627, $p < 0.001$), to have more sleep disorders (aOR = 1.474, $p = 0.024$) and to have lower medication adherence (aOR = 0.836, $p = 0.001$) independently of gender, current alcohol use disorder, second-generation antipsychotics and akathisia. No significant association was found for negative symptoms, childhood trauma and inflammation. More specifically, motivation deficits were associated with the following psychotic and depressive symptoms (Table S1): delusions, hallucinations, persecution, passive social withdrawal, somatic concern, anxiety, guiltiness, depression, unusual thoughts, impulsivity, active social withdrawal, subjective depressive mood, hopelessness, pathological guiltiness, self-depreciation, morning depression and suicidal ideation.

3.2. Variables potentially explained by severe motivation deficits (*Table 2*)

Severe motivation deficits were found to be significantly associated with the following variables independently of age and sex: functioning (GAF score $B = -0.194$, $p < 0.001$, PSP total score: $B = -0.159$, $p < 0.001$ (socially useful activities subscore only)), quality of life (S-Qol-18 total index score ($B = -0.486$, $p < 0.001$) and sentimental life, self-esteem, friendships, autonomy, psychological and physical well-being, resilience subscores), EQ5D-5L total score ($B = -0.437$, $p < 0.001$) (and for all EQ5D-5L domains:

Table 1. Model 1: variables potentially explained by severe motivation deficits (independent variable) in stabilised outpatients with schizophrenia.

	Univariate model			Multivariate model[a]	
Variables	No motivation deficit or mild to moderate motivation deficits $N = 326$ (58.1%)	Severe motivation deficits $N = 235$ (41.9%)	p	aOR (95% IC) or standardised beta	Adjusted p value[a]
Functioning					
Global Assessment of Functioning score	**53.26 (14.65)**	**47.73 (12.80)**	**<0.001**	**−0.194**	**<0.001**
PSP impaired professional functioning subscore	**0.70 (0.46)**	**0.1 (0.39)**	**0.002**	**0.124**	**0.005**
PSP impaired social functioning subscore	0.73 (0.44)	0.78 (0.41)	Ns		
PSP self neglect subscore	0.19 (0.39)	0.26 (0.44)	0.068	0.067	ns
PSP increased aggressiveness subscore	0.05 (0.21)	0.07 (0.26)	Ns		
PSP total score	**56.2 (15.9)**	**52.2 (15.5)**	**<0.001**	**−0.159**	**<0.001**
Quality of life					
Sentimental life (S-QoL subscore)	**41.89 (29.47)**	**26.05 (28.10)**	**<0.001**	**−0.258**	**<0.001**
Self-esteem (S-QoL subscore)	**59.65 (24.32)**	**32.84 (27.63)**	**<0.001**	**−0.455**	**<0.001**
Familial relationships (S-QoL subscore)	72.67 (23.17)	67.79 (27.70)	0.002	−0.081	0.056
Friendships (S-QoL subscore)	**57.82 (25.62)**	**45.45 (29.20)**	**<0.001**	**−0.211**	**<0.001**
Autonomy (S-QoL subscore)	**65.26 (23.59)**	**50.65 (27.31)**	**<0.001**	**−0.274**	**<0.001**
Psychological well-being (S-QoL subscore)	**64.74 (24.24)**	**41.32 (22.92)**	**<0.001**	**−0.044**	**<0.001**
Physical well-being (S-QoL subscore)	**56.17 (23.53)**	**29.63 (22.88)**	**<0.001**	**−0.492**	**<0.001**
Resilience (S-QoL subscore)	**64.12 (24.29)**	**45.44 (27.51)**	**<0.001**	**−0.330**	**<0.001**
Quality of Life (S-QoL Index score)	**60.29 (15.56)**	**42.41 (15.62)**	**<0.001**	**−0.486**	**<0.001**
Mobility (EQ5D subscore)	**1.26 (0.65)**	**1.52 (0.82)**	**<0.001**	**0.164**	**<0.001**
Autonomy (EQ5D subscore)	**1.13 (0.44)**	**1.38 (0.73)**	**<0.001**	**0.205**	**<0.001**
Activity (EQ5D subscore)	**1.66 (0.88)**	**2.64 (1.02)**	**<0.001**	**0.459**	**<0.001**
Pain (EQ5D subscore)	**1.70 (0.93)**	**2.18 (1.15)**	**<0.001**	**0.210**	**<0.001**
Anxiety/depression (EQ5D subscore)	**2.12 (1.00)**	**3.10 (1.18)**	**<0.001**	**0.406**	**<0.001**
Self-reported global health level (EQ5D subscore)	**71.04 (17.3)**	**52.02 (20.22)**	**<0.001**	**−0.448**	**<0.001**
Quality of Life (EQ5D total score)	**0.76 (0.20)**	**0.54 (0.24)**	**<0.001**	**−0.437**	**<0.001**
Outcomes associated with health-risky behaviour					
Body Mass Index (kg/m2)	26.63 (5.50)	26.57 (5.66)	Ns		
Metabolic syndrome	73 (27.9%)	50 (25.6%)	Ns		
Physical activity level (GPAQ score)	94.28 (152.29)	67.43 (135.04)	0.086	−0.085	ns
Current alcohol use disorder	**17 (10.2%)**	**25 (19.8%)**	**0.021**	**2.141 (1.120–4.093)**	**0.021**
Current tobacco smoking	168 (53.0%)	117 (52.2%)	Ns		
Severe nicotine dependence (among smokers only)	**35 (21.1%)**	**51 (45.1%)**	**<0.001**	**2.906 (1.681–5.024)**	**<0.001**
Current cannabis use disorder	22 (10.6%)	18 (11.5%)	Ns		
Clinical global impression score	**3.94 (1.35)**	**4.36 (1.18)**	**<0.001**	**0.162**	**<0.001**

BPAQ: Buss-Perry Aggression Questionnaire; CGI: Clinical Global Impression scale; MARS: Medication Adherence Rating Scale; PSP Professional and Social Functioning scale; SQoL-18: self-reported quality of life scale for schizophrenia.

[a]Adjusted for age and sex. The presented multivariate model includes the verbal aggression subscore of the BPAQ. All BPAQ subscores were tested in separate multivariate models to avoid multicollinearity, with no change in the results (data not shown).

The variables associated with severe motivation deficits in multivariate analyses ($p < 0.05$) are in bold. Ns: non significant ($p > 0.05$). The p values of variables with statistical tendency (p value between 0.05 and 0.10) were fully written.

mobility, autonomy, activity, physical pain, anxiety-depression and perceived global health status), alcohol use disorder (aOR = 2.141, $p = 0.021$), severe nicotine dependence (aOR = 2.906, $p < 0.001$), clinical global impression score (standardised beta(B): 0.162, $p < 0.001$). No significant association was found for body mass index, metabolic syndrome or physical activity level.

In subgroup analyses, all associations were maintained statistically significant except for PSP socially useful activity, which was not significant after removing patients with schizoaffective disorders or those with major depressive disorders ($p > 0.050$). The association between severe motivation deficit and respectively alcohol use disorders and S-QoL family relationships subscore became statistically significant after removing patients with major depressive disorders (aOR = 3.100, $p = 0.018$ and $B = -0.106$, $p = 0.030$) but not those with schizoaffective disorders ($p > 0.050$).

4. Discussion

In 561 stabilised patients with schizophrenia living in the community, we found that more than 40% reported severe motivation deficits. These deficits were associated with impaired socially useful activities but not social functioning and self-neglect. They were associated with the impairment of almost all domains of psychological and physical quality of life, alcohol

Table 2. Model 2: variables potentially explaining severe motivation deficits (dependent variable) in stabilised outpatients with schizophrenia.

	Univariate model			Multivariate model[a]	
Variables	No motivation deficit or mild to moderate motivation deficits $N = 326$ (58.1%)	Severe motivation deficits $N = 235$ (41.9%)	p	aOR (95% IC)	adjusted p value[a]
Sociodemographic and early life variables, *N* or Mean (% or SD)					
Age (years)	**30.55 (8.39)**	**32.35 (9.80)**	**0.023**	**1.031 (1.008–1.055)**	**0.008**
Gender (male)	175 (74.5%)	242 (74.0%)	Ns	1.195 (0.738–1.934)	Ns
Education level (years)	12.25 (2.70)	12.50 (2.55)	Ns		
Childhood trauma Questionnaire total score	40.82 (10.98)	41.73 (11.48)	Ns		
Age at schizophrenia onset (years)	21.10 (5.81)	21.35 (7.03)	Ns		
Age at first antipsychotic treatment (years)	22.34 (5.9)	22.98 (6.79)	Ns		
Age at first thymic episode (years)	21.38 (6.43)	20.32 (6.78)	Ns		
Lifetime number of thymic episodes	2.59 (2.32)	2.71 (2.70)	Ns		
Lifetime history of suicide attempts	**44 (14.0%)**	**78 (34.4%)**	**<0.001**	**2.297 (1.413–3.733)**	**0.001**
Current symptomatology N or Mean (% or SD)					
Positive symptoms (PANSS subscore)	**13.22 (5.30)**	**15.37 (6.18)**	**<0.001**	**1.052 (1.014–1.090)**	**0.006**
Negative symptoms (PANSS subscore)	18.25 (7.07)	18.93 (6.75)	Ns		
Current depressive episode (CDSS score $\geq$ 6)	**35 (10.9%)**	**85 (37.4%)**	**<0.001**	**2.627 (1.586–4.349)**	**<0.001**
Current manic episode (YMRS score $\geq$ 12)	4 (1.3%)	4 (1.8%)	Ns		
Current sleep disorder	**82 (25.2%)**	**106 (45.1%)**	**<0.001**	**1.474 (1.051–2.066)**	**0.024**
Current eating disorder	17 (9.2%)	18 (11.8%)	Ns		
Insight (Birchwood total score)	**8.8 (3.0)**	**9.4 (2.7)**	**0.001**	**1.104 (1.021–1.194)**	**0.013**
Insight of symptoms (Birchwood subscore)	**2.94 (1.22)**	**3.18 (1.12)**	**0.020**		
Insight of illness (Birchwood subscore)	**2.55 (1.43)**	**3.06 (1.19)**	**<0.001**		
Insight of treatment need (Birchwood subscore)	3.17 (1.00)	3.26 (0.91)	Ns		
Substance consumption and physical health, N (%)					
Current alcohol use disorder	17 (10.2%)	25 (19.8%)	0.021	2.020(0.947–4.309)	0.069
Current tobacco smoking	168 (53%)	117 (52.2%)	Ns		
Current cannabis use disorder	22 (10.6%)	18 (11.5%)	Ns		
Coffee consumption	195 (73.6%)	132 (69.5%)	Ns		
Current chronic physical disease	52 (40.6%)	36 (3.7%)	Ns		
Body Mass Index (kg/m2)	26.63 (5.50)	26.57 (5.66)	Ns		
Metabolic syndrome	73 (27.9%)	50 (25.6%)	Ns		
Hs-CRP level (mg/L)	2.90 (5.42)	2.88 (4.73)	Ns		
Treatments and treatment side-effects, N or Mean (% or SD)					
Second Generation Antipsychotics	189 (80.4%)	243 (74.3%)	0.090	0.880 (0.536–1.446)	Ns
Anticholinergic drugs	49 (15.0%)	41 (17.4%)	Ns		
Clozapine	51 (15.6%)	39 (16.6%)	Ns		
Antidepressants	81 (28.8%)	80 (42.1%)	0.003	1.294 (0.814–2.056)[a]	Ns
Mood stabilisers	40 (12.3%)	37 (15.7%)	Ns		
Benzodiazepine	58 (17.8%)	53 (22.6%)	Ns		
Extrapyramidal side-effects (SAS score)	0.27 (0.37)	0.26 (0.35)	Ns		
Akathisia (BAS score)	0.37 (0.80)	0.59 (0.99)	0.006	1.207 (0.967–1.508)	0.096
Sexual functioning score (men)	8.05 (5.85)	7.96 (5.16)	Ns		
Sexual functioning score (women)	7.57 (5.58)	8.11 (5.99)	Ns		
Medication adherence (MARS score)	**6.81 (2.21)**	**5.72 (2.00)**	**<0.001**	**0.836 (0.753–0.928)**	**0.001**

BAS: Barnes Akathisia Scale; CDSS: Calgary Depression Scale for Schizophrenia; MARS: Medication Adherence Rating Scale; PANSS: Positive and Negative Syndrome Scale; SAS: Simpson–Angus Scale; YMRS: Young Mania Rating Scale.

[a]As severe motivation deficits is here the variable to explain, all variables associated with severe motivation deficits with a p value <0.2 were included in the multivariate model. Antidepressant were strongly associated with current major depressive episode and could not be entered in the multivariate model because of colinearity. The multivariate results presented for antidepressants were extracted from a subanalysis replacing current major depressive episode by antidepressants (other associations remained significant in this alternative model).

The variables associated with severe motivation deficits in multivariate analyses ($p < 0.05$) are in bold. Ns: non significant ($p > 0.05$). The p values of variables with statistical tendency (p value between 0.05 and 0.10) were fully written.

use disorder and nicotine dependence. We found no significant association of motivation deficits with body mass index, metabolic syndrome or physical activity level. In the second model, motivation deficits were strongly associated with major depression, history of suicide attempt, current sleep disorders and low medication adherence. While positive symptoms and insight were marginally associated with motivation deficits, we found no association with negative symptoms, inflammation, antipsychotics or antidepressants treatments.

Motivation deficits were associated with almost all psychological and physical domains of quality of life of the FACE-SZ participants, which confirms that motivation deficits are one of the major unmet needs in real-world schizophrenia. We have reproduced previous findings underlying the strong association between motivation deficits and objective impaired

functioning, especially socially useful activities (Ang et al. 2020). Unemployment is a major pejorative outcome of schizophrenia (Tsang et al. 2010) and motivation deficits should therefore be specifically targeted during rehabilitation interventions. It should be underlined that these deficits were not associated with impaired objective social functioning or self-neglect in our results. This is an additional argument to distinguish goal-directed motivation from social motivation (Uchino et al. 2021).

These results add evidence for the complex relationships between alcohol, tobacco and motivation deficits (Bahorik et al. 2017; DeAtley et al. 2020). While most of the tobacco studies in schizophrenia were focussed on motivation to quit smoking, we found that severe nicotine dependence was strongly associated with goal-orientated motivation deficits in schizophrenia smokers. We also found that motivation deficits were associated with alcohol use disorders, replicating the results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (Bahorik et al. 2017). Motivation deficits should therefore be addressed in smoking cessation and alcohol reduction programs. On the contrary, the present results are not in favour of a role of motivation deficits in the success of weight loss or physical activity enhancement programs in schizophrenia.

The second model has yielded important directions for future motivation-enhancing programs.

First, the complex bilateral relationships between motivation and sleep, depression, suicide, and medication adherence has been explored outside schizophrenia but only in a one-to-one basis (Kenney et al. 2013; Russell et al. 2018; Liverant et al. 2021). The present study is the first to gather these factors that should be further explored in prospective follow-up studies and interventions. This model suggests that sleep, depression, suicide, medication adherence and positive symptoms play independent roles and that each of these factors should be targeted to address motivation deficits. The role of depression and sleep in motivation is well known outside schizophrenia. However, we found that our results were maintained in patients without major depressive disorders or schizoaffective disorders, confirming that mood do not explain all motivation deficit issues. The association between medication adherence and motivation deficits independently of the previous factors may be explained by decreased motivation to take medications or by the subjective negative side effects of the treatments (Misdrahi et al. 2016). While clozapine decreases positive symptoms and suicide (three factors associated with motivation deficits in our results), patients treated with clozapine were not found to have less motivation deficits than clozapine-free ones. Based on our results, no treatment seems to be associated with increased or decreased motivation deficits, even antidepressants that were previously suggested to be effective on negative symptoms (Rummel et al. 2006). Contrary to our expectations, we found no association of motivation deficits with the PANSS negative factor. More specifically, motivation deficits were only associated with social withdrawal. Our results are therefore in favour of the hypothesis that motivation deficits and negative symptoms are underpinned by different pathophysiological substrates and with different relations to outcomes and that depression and sleep better explain motivation deficits than negative symptoms (Kimhy et al. 2006; Galderisi et al. 2013).

These results should be taken with caveats as they are cross-sectional. However, they yield important clues to developed precision medicine-based motivation enhancing programs in schizophrenia. There is currently a major gap between the unmet need to address motivation deficits in schizophrenia in clinical practice (supported by our results) and the lack of research and guidelines in the field. There is no mention of motivation deficits in the last updates of the World Federation of Societies of Biological Psychiatry (WFSBP) and the National Institute for Health and Care Excellence (NICE) guidelines for schizophrenia (NICE clinical guideline 2014), even in the 'special circumstances' guidelines including depression, suicidality, substance use disorders, pregnancy and lactation (Hasan et al. 2015). We suggest that a specific chapter could be added in the next update. We carried out a pubmed research review with the search paradigm 'Schizophrenia AND (motivation or avolition)' (28th May 2021). Among pharmacological approaches, roluperidone (Strauss et al. 2019; Harvey et al. 2020), rasagiline (Buchanan et al. 2015), minocycline (Kelly et al. 2015; Krynicki et al. 2021) and oxytocin (Bradley et al. 2020) have been explored in small sample size randomised trials with no clinical applications in daily practice so far. Among other interventions, motivational interview, behavioural activation, smartphone intervention, incentives and informationally administered rewards and neurostimulation have shown promising but still preliminary results (Prikryl et al. 2013; Hager et al. 2015; Schlosser et al. 2018; Hunt et al. 2019; Luther et al. 2020; Bodén et al. 2021; Brandt et al. 2021). In our sample, motivation decreases with age, suggesting that clinicians should implement

interventions (regardless of their type) early in the illness course to prevent motivation deficits.

4.1. Strengths

This study is the first study to include such a wide range of clinical and treatment factors to explore motivation deficits in schizophrenia. All patients were evaluated with a standardised battery. The national area of recruitment of 10 centres limited the selection bias. All evaluators were trained in the FondaMental Schizophrenia Expert Network, with regular training sessions (at least once a year) for the clinicians-rated scales (Fond et al. 2020). Our depression and functioning evaluations were objective/clinician-rated evaluations. It is therefore unlikely that depressive symptoms may have influenced the patients' perception of their own functioning contrary to previous works leading to artefactual associations. We have chosen the most severe level of motivation deficits to define the motivation deficits group. Despite this stringent threshold, we identified more than 40% of the patients reporting severe motivation deficits.

4.2. Limits

These results are cross-sectional and no causal relationship can be inferred. The next step will be to explore the impact of motivation deficits on illness trajectory during follow-up. Our results push for the need of an adequate dedicated scale to evaluate motivation in schizophrenia, distinguishing goal-directed activities from social activities. We found no significant associations of physical activity with motivation deficits in our analyses. However preliminary data suggests that aerobic exercise may increase motivation in schizophrenia (Shimada et al. 2019) and accurate physical activity assessment is complex with discrepancies between objective and subjective measurements. We also found no argument for inflammation to play a role in motivation deficits in stabilised treated outpatients. We used only hs-CRP as inflammatory marker. Other markers like IL-6 may be more relevant to explore this association (Al-Hakeim et al. 2015), but it is not available in daily clinical practice. The association of depression, suicide and motivation deficits suggests also a potential role of self-stigma that has not been captured in the FACE-SZ database and should be investigated.

5. Conclusion

Motivation deficits are frequent and remain persistent unmet need in real-world schizophrenia that should be addressed in future guidelines. Based on our results, literature and clinical experience, we recommend to address in priority major depression, sleep, suicide, positive symptoms (when present and as early as possible) and medication adherence to improve motivation deficits of schizophrenia.

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Author contributions

LB performed the statistical analysis. TK, LB and GF wrote the first complete manuscript. All authors were involved in the patients' recruitment, the clinical evaluation, acquisition of the clinical data, modified the manuscript and approved the final version.

Statement of interest

None to declare.

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