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Towards an improved access to psychiatric rehabilitation: availability and effectiveness at 1-year follow-up of psychoeducation, cognitive remediation therapy, cognitive behaviour therapy and social skills training in the FondaMental Advanced Centers of Expertise-Schizophrenia (FACE-SZ) national cohort. Running title: Psychosocial therapies in schizophrenia PhD and the FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) group*

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HAL Id: hal-02473263

<https://amu.hal.science/hal-02473263v1>

Submitted on 10 Feb 2020

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► **To cite this version:**

Julien Dubreucq, Bernard Ycart, F. Gabayet, C. Perier, Agnès Hamon, et al.. Towards an improved access to psychiatric rehabilitation: availability and effectiveness at 1-year follow-up of psychoeducation, cognitive remediation therapy, cognitive behaviour therapy and social skills training in the FondaMental Advanced Centers of Expertise-Schizophrenia (FACE-SZ) national cohort. Running title: Psychosocial therapies in schizophrenia PhD and the FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) group*. *European Archives of Psychiatry and Clinical Neuroscience*, 2019, 269 (5), pp.599-610. 10.1007/s00406-019-01001-4 . hal-02473263

Towards an improved access to psychiatric rehabilitation: availability and effectiveness at 1-year follow-up of psychoeducation, cognitive remediation therapy, cognitive behaviour therapy and social skills training in the FondaMental Advanced Centers of Expertise-Schizophrenia (FACE-SZ) national cohort.

Running title: Psychosocial therapies in schizophrenia

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WORD COUNT

ABSTRACT: 296

WORD COUNT: 3536

ABSTRACT

Background: Psychosocial Interventions (PIs) have shown positive effects on clinical and functional outcomes of schizophrenia (SZ) in randomized controlled trials. However their effectiveness and accessibility remain unclear to date in “real world” schizophrenia.

Objectives: (i) To assess the proportion of service users with SZ who received PIs between 2013 and 2015 in France after an Expert Center intervention in a national multicentric non-selected community-dwelling sample; (ii) to assess PIs effectiveness at one-year follow-up.

Methods: 183 SZ outpatients were recruited from FondaMental Advanced Centers of Expertise for Schizophrenia cohort and followed-up at one year. Baseline and one-year evaluations included sociodemographic data, current treatments, illness characteristics, addictive behaviors and standardized scales for clinical severity, adherence to treatment, quality of life, a large cognitive battery, and daily functioning assessment.

Results: 64 (35%) of the 183 participants received at least one PI during the one-year follow-up. Having had at least one PI has been associated in multivariate analyses with significantly higher improvement in positive and negative symptoms (respectively $p=0.031$; $p=0.011$), mental flexibility (TMT B, $p=0.029$; C-VF, $p=0.02$) and global functioning ($p=0.042$). Cognitive behaviour therapy (CBT) and social skills training (SST) were associated with higher cognitive improvements (in speed of processing and mental flexibility), while cognitive remediation (CRT) was associated with clinical improvement, beyond cognitive symptoms. These results have not been demonstrated before and suggest that the effect of each PI is larger than its initial target (i.e. positive/negative symptoms for CBT, cognition for CRT).

Conclusion: The present study has confirmed the PIs’ effectiveness in a large sample of community-dwelling SZ outpatients at one year follow-up. Efforts to improve access to PI should therefore be reinforced in public health policies.

Keywords: Schizophrenia, rehabilitation, psychosocial interventions, effectiveness, functioning

Introduction

The concept of recovery has begun to transform practices and mental health systems throughout the world, switching from symptom-reduction to improved functioning and quality of life outcomes (Slade et al., 2014). Recovery may be defined either from a clinical perspective (i.e. clinical and functional remission) or from a consumer-oriented one, as a self-broadening process aiming at living a meaningful life beyond mental illness (Roe et al., 2011). In a recent meta-analysis, only 13.5% of the persons with schizophrenia (SZ) met the criteria for clinical recovery (Jääskeläinen et al., 2013).

A growing bundle of evidence suggests that this proportion could be deeply improved by Psychosocial Interventions (PIs) including psychoeducation (PSE), cognitive remediation therapy (CRT), cognitive behaviour therapy (CBT) and social skills training (SST). PSE has shown effectiveness in reducing psychotic relapse rates and medication non-adherence (Xia et al., 2011). CRT has shown effectiveness in improving cognitive and psychosocial functioning (MacGurk et al., 2007; Wykes et al., 2011). CBT has shown effectiveness in positive and negative symptoms and psychosocial functioning (Wykes et al., 2008). SST has shown improvement on social and daily living skills, community functioning, negative symptoms and relapses (Kurtz et Mueser, 2008). All PIs appear to remain effective at one-year follow-up (Xia et al., 2011; MacGurk et al., 2007; Wykes et al., 2011; Wykes et al., 2008), except for SST where it is less clear due to a lack of follow-up data (Kurtz et al., 2008). In summary, each PI has shown some effectiveness in specific domains, but no longitudinal study has evaluated their global effectiveness in real-world conditions (Meneer et Briand, 2014). Moreover, PIs remain poorly available to service users with SZ in Western Countries: in 2010 only 15% of the 6007 participants with SZ in the French cohort ESPASS (Leguay et al., 2010) and 36.5% of the 1825 persons with SZ in the 2nd Australian National Survey (Morgan et al.,

2012) were engaged in any form of psychosocial rehabilitation (including PIs, family interventions and sheltered or competitive employment).

The objectives of the present study were: (i) to assess the proportion of service users who received PIs between 2010 and 2015 in France after an Expert Center Intervention in a national multicentric non-selected community-dwelling SZ sample; (ii) to assess PIs effectiveness at one-year follow-up.

2. Material and methods

2.1. Study population

The FACE-SZ cohort is based on an ongoing French national network of schizophrenia Expert Centers that has been extensively described in a previous article (Schürhoff et al., 2015). Service users are referred to Expert Centers by their general practitioner or psychiatrist, who remains in charge of routine care and treatment. Patients are yearly followed-up at the Expert Center and at the end of each evaluation a detailed evaluation report is sent to the patient and the referrer along with a personalized care program multifaceted and including the rationale for PI recommendation. The appraisal protocol was approved by the relevant Ethical Review Board (CPP-Ile de France IX) on January 18, 2010. All participants gave their written informed consent.

2.2. Data collected

General information on education, marital status, economic status, illness onset and trajectory and comorbidities, was recorded. Illness severity was assessed using the Positive and Negative Syndrome (PANSS) (Kay et al., 1987) and the Clinical Global Impression (CGI) scales (Haro et al., 2003). Current depressive symptoms were evaluated using the Calgary Depression Rating Scale for Schizophrenia (CDSS) (Addington et al., 1993). Insight was

measured both with a self-reported measure (Birchwood Insight Scale; BIS) (Birchwood et al., 1994) and with the clinician-rated Scale to assess Unawareness of illness in Mental Disorders (SUMD) (Amador, 1990). Adherence into treatment was self-reported with the Medication Adherence Rating Scale (MARS) (Thompson et al., 2000) therapeutic observance being evaluated by clinicians with the Brief Adherence Rating Scale (BARS) (Byerly et al., 2008). Quality of Life was evaluated with the self-reported Subjective Quality of Life scale (S-QoL) (Auquier et al., 2003). General Functioning was measured with the Global Assessment of Functioning scale (GAF) (Startup et al., 2002). Neuropsychological baseline and one year cognitive assessments included verbal fluency (L-VF; C-VF) (Godefroy et le GREFEX, 2008) for spontaneous mental flexibility, Trail Making Test A and B (TMT-A or B)) (Godefroy et le GREFEX, 2008) respectively for speed of processing and reactive mental flexibility, Continuous Performance Test-Identical Pair version (CPT-IP) (Cornblatt et al., 1988) for sustained attention implying working memory mechanisms and premorbid IQ with the French-National Adult Reading Test (f-NART) (Mackinnon et Mulligan, 2005). To avoid test-retest effects, Intelligence Quotient (IQ) was assessed only at baseline with Wechsler Adult Intelligence Scale-4th edition (WAIS-IV) (Wechsler, 2008).

Psychosocial intervention definition

The “PI+” group was defined as service users following at least one PI during the one-year follow-up among manualized and standardized group psychoeducation (PSE), group cognitive behaviour therapy (CBT), group social skills training (SST) and individual and group cognitive remediation therapy (CRT) (Khazaal et al., 2015; Briki et al., 2014; Franck et al., 2013; D’Amato et al., 2011; Roder et al., 2011; Twamley et al., 2012; Bazin et al., 2010). Beginning and ending dates of interventions were systematically recorded and only participants who completed at least 75% of the sessions were considered as PI+.

2.3. Statistical Analysis

Clinical and functional outcomes were compared at baseline (“V0” visit) and after one year of follow-up (“V1”). For each outcome variable, improvement was defined as the difference between the values at V0 and V1, oriented so that a positive difference should correspond to an improvement of the patient’s condition. Each difference was adjusted by a linear regression over its confounding value at V0. Seventeen variables of interest were chosen: positive, negative, general psychopathology subscale scores and total score for PANSS, scores of the CDSS, CGI, GAF, S-QoL, BIS, and MARS, awareness and attribution scores of SUMD, number of words in the two verbal fluency tests, time at the TMT A and B, and d prime score in the fourth condition of the CPT-IP.

In the univariate analysis, the seventeen adjusted differences were compared to having had or not CBT, CRT, PSE, SST; having had or not at least one PI; the one-sided Student T-test was used. The one-sided correlation test between the seventeen adjusted improvement variables and the number of PIs was also computed. Results are shown on Table 2.

In the multivariate analysis, the same seventeen adjusted improvements were considered as responses. Having had or not at least one PI was retained as a predictor. The values at V0 of the seventeen variables of interest were considered as covariates. Fifteen factors were added: (age at V0, age at first episode, level of education, memory score, IQ, gender, housing (independent or not), professional status (unemployed or not), diagnosis (schizophrenia vs. schizo-affective disorder), psychotic episodes, suicide attempts and full time hospitalizations during past year, alcohol and cannabis consumptions, treatment type (second generation vs. first generation antipsychotics)). Thus improvement for each variable of interest was tested against a set of thirty-three potentially explanatory factors, including the predictor. Univariate significance p-values were computed, and covariates significant at the 10% level were

included in a regression model. Exhaustive variable selection determined the best model in the sense of adjusted R-squared.

Data was analysed using the R software, version 3.2.3 (Wechsler, 2008). The psych package version 1.5.8, was used (R Core Team, 2015). Effect Size (Cohen's d) was calculated using package effsize (Revelle, 2015). Size effects inferior to 0.20 were considered as negligible, from 0.20 to 0.40 as small, from 0.40 to 0.60 as moderate and superior to 0.60 as strong (Revelle, 2015). For variable selection, the leaps package version 2.9 was used (Lumley, 2009). The level of confidence intervals was set at 0.95, and the significance level of tests was set at 0.05. The initial data set had 9.23% missing data on average, over 54 variables of interest. The multivariate imputation method described in (Van Buuren, 2012) was applied, using the package mice (Van Buuren et Groothuis-Oudshoorn, 2012). Statistical treatments were first conducted using the standard pairwise deletion method, then repeated over 100 imputed datasets. The tables report p-values from the pairwise deletion method; only conclusions remaining consistent through most imputed datasets were considered as significant.

3. Results

Overall, 183 stabilized SZ outpatients were included in the 10 centers of the FACE-SZ national cohort and followed-up for one year. The sample included mostly men (144, 78.7%), with a mean age of 33.9 (SD=10.26) years, mean illness duration of 11.1 (SD=9.19) years and a mean baseline PANSS total score of 69.9 (SD=17.38). Baseline sample characteristics are shown on Table 1. At inclusion, 7 (3.8%) patients had received at least one PI (CRT N=4, CBT N=2, SST N=1). Removing these patients did not change the results (data not shown).

64 (35%) had received at least one PI during the follow-up period: CRT (N=36, 19.7%), CBT (N=29, 15.8%), PSE (N=31, 16.9%) and SST (N=18, 9.8%). Overall, those with higher

baseline insight scores ($p=0.007$), better cognitive function and higher depressive symptoms ($p=0.017$) accessed more to at least one PI during the one-year follow-up. No clinical variable at baseline was associated with a specific PI except for higher depression level that was associated with CBT ($p=0.017$) (table 1).

In the univariate analyses, having had at least one PI during the one-year follow-up has been significantly associated with improvement in negative symptoms (PANSS negative; $d=0.44$; $p=0.003$), insight (BIS; $d=0.42$; $p=0.004$), sustained attention/working memory (CPT-IP; $d=0.48$; $p=0.023$) and spontaneous and reactive mental flexibility (C-VF; $d=0.57$; $p<0.001$; TMT B; $d=0.58$; $p=0.001$) (Table 2). It was also correlated to mild improvements in positive symptoms (PANSS positive score; $d=0.31$; $p=0.021$), adherence to treatment (MARS; $d=0.35$; $p=0.024$) speed of processing (TMT A; $d=0.30$; $p=0.044$) and global functioning (GAF score; $d=0.37$; $p=0.012$).

PSE was associated with a moderate improvement of adherence into treatment (MARS score; $d=0.53$, $p=0.006$) and improvement in psychotic symptomatology (PANSS total score, $d=0.47$, $p=0.008$).

CBT has been associated with moderate improvement in global functioning (GAF score, $d=0.59$, $p=0.001$), spontaneous mental flexibility (C-VF, $d=0.58$, $p=0.003$) clinical global severity (CGI, $d=0.46$, $p=0.010$) and to mild improvement in positive symptoms ($d=0.34$, $p=0.026$) and speed of processing (TMT A, $d=0.34$, $p=0.012$). CBT was however also associated with decreased quality of life (S-QoL, $p=0.973$).

CRT has been associated with high improvement in reactive mental flexibility (TMT-B, $d=0.77$, $p<0.001$) and with moderate improvement of other cognitive processes (sustained attention / working memory CPT-IP; $d=0.45$; $p=0.019$; spontaneous mental flexibility C-VF; $d=0.49$ $p=0.006$) and both positive ($d=0.42$, $p=0.007$) and negative ($d=0.47$, $p=0.005$) symptoms. CRT was also found to have a mild effect on clinical global severity (CGI score

d=0.36 p=0.022) and on the level of insight into illness (SUMD awareness score d=0.38 p=0.023; SUMD attribution score d=0.42 p=0.011).

SST has been associated with moderate improvements in clinical severity (CGI score, d=0.44 p=.015), spontaneous and reactive mental flexibility (C-VF; d=0.55 p=0.015; TMT B d=0.47 p=0.006) and global functioning (GAF; d=0.46 p=0.005). Mild improvements have also been found on negative symptoms (d=0.25 p=0.044) and speed of processing (TMT A; d=0.38 p=0.024). SST was however also associated with decreased quality of life (S-QoL, p=0.856).

In the multivariate analysis, having had or not at least one PI was retained as the main explanatory factor for the improvement of positive (p=0.031) and negative (p=0.011) symptoms PANSS scores, clinical global severity CGI score (p=0.003), spontaneous and reactive mental flexibility (C-VF; p=0.002; TMT B, p=0.029) and global functioning GAF score (p=0.042).

4. Discussion

Altogether, the findings of the present study may be summarized as follows:

(i) compared to the very low rates of service users with SZ benefiting from PIs outside of the Expert Centers network (12% of the 6007 participants in the 2010 ESPASS study (Leguay et al., 2010); 3.8% during the 12 months before evaluation in the present study), PIs were more frequently offered and delivered in the FACE network between 2010 and 2015 (35%).

(ii) In a large sample of non-selected community-dwelling SZ service users followed-up during one year, those who received one of the 4 PIs improved significantly more on clinical symptomatology, mental flexibility and functioning at one year compared to those who did not. Moreover, CBT and SST have been associated with higher cognitive improvements (in speed of processing and mental flexibility), while CRT was associated with clinical improvement, beyond cognitive symptoms. These results have not been demonstrated before

and suggest that the effect of each PI is larger than its initial target (i.e. positive/negative symptoms for CBT, cognition for CRT).

As mentioned in the rationale, the access to PIs was extremely low in France before the development of the FACE-SZ network in 2009. Only 15% of the 6007 participants with SZ included in the ESPASS cohort were engaged in any form of psychosocial rehabilitation (including the 4 PIs, family interventions and sheltered or competitive employment) during the 6-months follow-up period; only 2% received CBT; 1% CRT; 2% SST and 7% PSE (Leguay et al., 2010). Similarly, only 3.8% of the participants included in the FACE cohort had received from at least one PI on the year before evaluation. Several barriers to the implementation of evidence-based interventions in routine clinical practice have been identified in the literature- including lack of available resource (Ince et al., 2016) lack of specific training (Ince et al., 2016; Kimhy et al., 2013), lack of dedicated time to perform interventions (Kimhy et al., 2013), excessive caseloads for a limited workforce capacity (Ince et al., 2016), staff members lack of knowledge about PIs and their efficacy (Ince et al., 2016; Kimhy et al., 2013), negative management and team attitude towards PIs (Kimhy et al., 2013), lack of service users sharing the same diagnosis for structured psychoeducation (Getachew et al., 2009) and difficulties to identify those who would need an intervention for CBT (Ince et al., 2016). One of the aims of the FACE-SZ expert center network is to widespread psychosocial interventions by increasing access to a comprehensive evaluation, to trained psychologists and to a personalized recovery-orientated plan of care. The present results suggest that expert center network is effective in increasing the rate of PIs delivery.

More specifically, 15.8% of the 183 participants included in the present sample received CBT during the follow-up period. This is higher than the proportion found in UK in 2014 (5.3% of 187 participants) (Haddock et al., 2014) but it remains less developed compared to

Australia (22.3% of 1825 participants) (Morgan et al., 2012). The development of a large Australian PI network since the 2000s beyond the national public health system in this country may explain this difference (Morgan et al., 2012). Access to PSE (16.9% in the present sample) was higher compared to the 2010 ESPASS study (7%) (Leguay et al., 2010) but PSE is still less available than in German-speaking countries (21% of 338 participants in 2003) (Rummel-Kluge et al., 2006). In these countries, PSE has been included in the national mental health policy. The proportion of service users who have received CRT and SST in the present study was much higher compared to the ESPASS 2010 study (Leguay et al., 2010) (respectively 19.1% vs. 1% for CRT and 9.8% vs 2% for SST). To the best of our knowledge, no comparative data has been published for other countries.

CBT is the most documented intervention regarding its effectiveness, access rates and implementation in national policies (Menear et Briand 2014; Ince et al., 2016; Kimhy et al., 2013; Lewis et al., 1981). CBT has been associated in the present sample with improvements in positive symptoms but not negative symptoms, consistently with the findings of a previous study ($d=0.37$ (Wykes et al., 2008) vs. $d=0.34$ in the present study). Moreover, CBT has been independently associated with improvements in speed of processing and mental flexibility in the present results, which has not been demonstrated before. Improvements in speed of processing has been previously associated in recent studies with functional change during psychosocial rehabilitation (Rispaud et al., 2016) and to participation in community activities (Lepage et al., 2014). Improved mental flexibility has been associated with better functional outcomes (Lepage et al., 2014). Future studies should determine whether improvement in cognitive functions mediates the relationship between CBT and the improvement in global functioning. The effect size of the improvement of global functioning associated with CBT was larger in the present study compared with previous studies ($d=0.59$ in the present study vs. 0.38) (Wykes et al., 2008). The factors associated with effectiveness of CBT on global

functioning in service users with SZ should be explored in future studies. SST has shown moderate effects on global functioning in the present study, which is consistent with the results of a previous study (Kurtz et Mueser, 2008), ($d=0.52$ vs. $d=0.46$ in the present sample), however the effect size on negative symptoms was smaller in the present study ($d=0.25$ vs. $d=0.40$) (Kurtz et Mueser, 2008). SST was also associated with mild improvements in speed of processing and moderate improvements in mental flexibility in the present study. Speed of processing has been recently described as a mediator of social competence, interpersonal relationships and community functioning (Rispaud et al., 2016; Lepage et al., 2014). Mental flexibility has also been associated with social functioning and problem solving (Lepage et al., 2014). Further studies should determine if the effect of SST on global functioning is mediated by the improvement in negative symptoms, social cognition (Varga et al, 2018), speed of processing and/or mental flexibility. Despite improved cognitive and symptoms outcomes CBT and SST appeared to worsen subjective quality of life. This might be linked to improved insight into illness and to increased awareness of their difficulties (Margariti, 2014).

The present results suggest that PSE is associated with the improvement in adherence into treatment and clinical severity at one year, consistently with a previous study (Xia et al., 2011).

Consistently with some studies (MacGurk et al., 2007; Wykes et al., 2011), CRT has shown a moderate positive effect on cognitive functioning in the present study ($d=0.42-0.77$ vs. $d=0.36$ (MacGurk et al., 2007); $d=0.42$ (Wykes et al., 2011)). CRT has been also associated in the present sample with moderate improvements in negative symptoms ($d=0.47$). This is consistent with the literature, although reported effects-sizes were smaller in a recent meta-analysis (Hedge's $g=0.30$) (Cella et al., 2017). Future studies should determine whether improving executive functions might mediate the association between CRT and negative symptoms reduction, as suggested in a previous study (Farreny et al., 2013). This effect may

be mediated by specific CRT modules or by non-specific ones (e.g. contact with a therapist or attendance to sessions) (Vinogradov et al., 2013). In contrast with other studies (MacGurk et al., 2007; Wykes et al., 2011), CRT has however not been associated with improvement in global functioning in the present sample ($p>0.05$). Future studies should determine the parameters associated with the CRT effectiveness.

Limits: Although the network of FondaMental Experts Center for Schizophrenia covers the whole French territory, it cannot be definitely asserted that the FACE-SZ database contains a representative sample of the French population of schizophrenic patients. However, some sample characteristics (including sex ratio, age at illness onset, comorbidities) suggest that the present sample may be compared to general stabilized community-dwelling SZ population. Institutionalized or very disabled patients are not able to receive a 2-day long comprehensive evaluation and were therefore not represented in the present sample, which limits the extrapolation of the present results to this population, as well as to patients younger than 16 years.

Strengths. Compared to the previous studies mentioned in the rationale, the present study exhibits clear strengths: a large non-selected sample of community-dwelling SZ outpatients, the use of a large bundle of standardized evaluation scales, and the inclusion of a large number of potential confounding factors in the multivariate analysis.

Conclusion

Psychosocial interventions have been associated with a large bundle of improvements in the present sample of SZ community-dwelling service users. Each therapy has shown effectiveness on its primary target (e.g. cognition for CRT, psychotic symptomatology for CBT) but also effectiveness on other dimensions (e.g. cognition for CBT, negative symptoms for CRT). The largest global effects of PIs were found for negative symptoms, sustained

attention / working memory and mental flexibility. Future health policies should determine which PI should be systematically proposed to each patient in a personalized/precision medicine approach to optimize accessibility, patient's adherence and effectiveness.

ACKNOWLEDGEMENTS

Acknowledgments and funding source. This work was funded by AP-HP (Assistance Publique des Hôpitaux de Paris), Fondation FondaMental (RTRS Santé Mentale), by the Investissements d'Avenir program managed by the ANR under reference ANR-11-IDEX-0004-02 and ANR-10-COHO-10-01, and by INSERM (Institut National de la Santé et de la Recherche Médicale). We express all our thanks to the nurses, and to the patients who were included in the present study. We thank Hakim Laouamri, and his team (Stéphane Beaufort, Seif Ben Salem, Karmène Souyris, Victor Barteau and Mohamed Laaidi) for the development of the FACE-SZ computer interface, data management, quality control and regulatory aspects. We thank also Isabelle Durand-Zaleski and Amélie Prigent from URC-Eco IDF for their precious advices.

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Author contribution statement: The authors had full access to the data in the study and take the responsibility for the integrity of the data and the accuracy of the data analysis. Dr Julien Dubreucq drafted the article and made the literature review. Pr Bernard Ycart and Mrs Agnès Hamon performed the statistical analysis. Dr Guillaume Fond, Pr Pierre Michel Llorca, M. Franck Gabayet and Mrs Claire Cécile Périer contributed to the interpretation of data and critically revised the article. All the authors were involved in the collection and analysis of the data. All authors contributed to and have approved the final manuscript.

Conflicts of interest: none declared

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