In Patients with Schizophrenia Symptoms Improvement can be Uncorrelated with Quality of Life Improvement

Kayigan Wilson-d’Almeida1,2, Karow Anne3, Marie-Cécile Bralet1,2,4, Nadine Bazin5,6, Marie-Christine Hardy-Baylé5,6, Bruno Falissard1,2,7

1Inserm, U669, Paris, France;
2Univ Paris-Sud and Univ Paris Descartes, UMR-S0669, Paris, France;
3Universitätsklinik Hamburg-Eppendorf, Hamburg, Germany;
4CHS Clermont de l’Oise, France;
5Univ Versailles Saint-Quentin, EA 4047, Versailles, France;
6Centre Hospitalier de Versailles, Versailles, France;
7AP-HP, Hôpital Paul Brousse, Département de santé publique, Villejuif, France.

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Kayigan Wilson-d’Almeida
INSERM U669
Maison de Solenn
97 Boulevard du Port-Royal
75679 Paris Cedex 14
France
kayialmeida@hotmail.com
Tel: (33) 1 58412850
Fax: (33) 1 58412843

Karow Anne
Universitätsklinik Hamburg-Eppendorf
Zentrum für Psychosoziale Medizin, Psychiatrie und Psychotherapie
Martinistr. 52,
20246 Hamburg, Germany
karow@uke.uni-hamburg.de
Tel/fax: (49)-40-42803-2242
Marie-Cécile Bralet
INSERM U669
Maison de Solenn
97 Boulevard du Port-Royal
75679 Paris Cedex 14
France
mariemarthebralet@yahoo.fr
Tel: (33) 1 58412850
Fax: (33) 1 58412843

Nadine Bazin
Service de Psychiatrie,
Hôpital Richaud,
1, rue Richaud,
78000, Versailles, France
NBAZIN@ch-versailles.fr
tél : (33) 1 39 63 90 10
fax : (33) 1 39 50 50 93

Marie-Christine Hardy-Bayle
Service de Psychiatrie,
Hôpital Richaud,
1, rue Richaud,
78000, Versailles, France
mchardybayle@ch-versailles.fr
tél : (33) 1 39 63 90 10
fax : (33) 1 39 50 50 93

Corresponding author
Bruno Falissard
INSERM U669
Maison de Solenn
97 Boulevard du Port-Royal
75679 Paris Cedex 14
France
Email : falissard_b@wanadoo.fr
Tel: (33) 6 81827076
Fax: (33) 1 58412843
Conflict of interest

Bruno Falissard has consulted for Servier, Eli Lilly, SANOFI-Aventis, Roche, Genzyme. All other authors declare that they have no conflicts of interest.

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Abstract

Objectives: Quality of life has been found to be associated to symptoms in patients with schizophrenia. Nevertheless, the mechanism that underlies that association is still unclear. The objective of this paper is to prospectively evaluate quality of life of patients with schizophrenia in relation with the joint evolution of their symptoms, their expectations and their perceived position in life.

Methods: Participants included 306 outpatients with schizophrenia who were interviewed at baseline, 6 and 12 months, about their quality of life (Outcome revealed by Preference in Schizophrenia, OPS) and symptoms (Positive and Negative Syndrome Scale, PANSS).

Results: Quality of life relative to subject expectations remained stable over time. A decrease in symptoms was correlated to an increase in both expectations and perceived position in life but did not correlate to quality of life.

Conclusion: The level of expectations seems to play a major role in the subjective assessment of quality of life in patients with schizophrenia. Symptoms improvement is not necessarily associated with quality of life improvement relative to subject expectation. Caregivers should be aware of this result to deal with possible disappointments in patients receiving a new efficient treatment.

Keywords: quality of life; patients’ expectations; symptoms; position in life

1. Introduction
For a long time, the wide variety of outcomes used in medical research did not take the patient's opinion into account and focused instead on clinical symptoms, hospitalization, mortality, social and occupational functioning or social support. Health-related quality of life measurement has however received progressively increasing attention in medicine [22]. This has led to individuals’ perceptions being introduced into the assessment of medical care, in a “medicine for the person” perspective [13].

If there is no doubt that this field is at the moment of a great importance, it nevertheless appears rather imprecise on a conceptual point of view. First, it is not easy to define what is “quality of life” and even “health-related quality of life”. If the proposition made by the WHO (World Health Organisation) “individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns” [13] sounds well, it seems difficult to operationalize simply in practice. Second, there is a competition between concepts. Health-related quality of life is challenged, in particular, by the notions of disability and recovery.

Concerning disability, WHO [25] defines it as “an umbrella term for impairments, activity limitations, and participation restrictions. Disability refers to the negative aspects of the interaction between individuals with a health condition (such as cerebral palsy, Down syndrome, depression) and personal and environmental factors (such as negative attitudes, inaccessible transportation and public buildings, and limited social supports).” Here, disability is not limited to the classical and objective notion of functional impairment since it refers to the position of a human being in a given society. Disability is thus basically a subjective notions and it is obviously related to what common sense defines as quality of life.

About recovery, it appears as a polysemous term with a meaning situated between two extremes [18]: 1/ a fully operationalized notion which combine symptoms, functioning and duration of a positive evolution and 2/ an existentialist notion where a subject with a chronic
illness overcomes his or her condition of patient “including poverty, stigma, demoralization, hopelessness and social isolation.” Recovery is therefore related to disability (through stigma for instance) and to quality of life (through demoralization and hopelessness in particular).

Quality of life, disability, recovery are three concepts entangled one with the others and it is thus necessary to precise here what will be tackled in the present paper. We will consider quality of life according to Calman’s perspective: the subjective gap between a person’s expectations and achievements [3]. In accordance with this definition, quality of life will be assessed using an instrument based on a methodology of revealed preference: the Outcome revealed by Preference in Schizophrenia (OPS) [7]. In this instrument, patients are asked to position themselves over a range of situations and the score obtained gives an indirect quantification of the level of acceptability of their own existence according to their expectations. The notion of expectation is basically phenomenological here (phenomenological is used at this point with the meaning given by the German and French philosophical tradition [20]). In other words, the subject expresses, with a full consciousness and with a first person point of view, which life situation could be considered or not as acceptable.

Three scores are obtained from this instrument. The first score is related to the level of expectations of the patients (the higher the score, the higher the expectations). The second score is related to the perceived position in life of patients (the higher the score, the better the patients’ opinion concerning his/her own life). Finally, the third score is obtained by subtracting the first score from the second. This last score reflects the patients’ position in life relative to their expectations. In other words this score reflects the quality of life as defined by Calman: a high score for a patient means that his perceived position in life is much higher than his expectations.
The objectives of the present study were to prospectively evaluate quality of life in patients with schizophrenia and to analyze its clinical correlate using the OPS instrument. We hypothesized that, when engaged in a new treatment, incompletely stabilized patients improve their symptoms, raise their level of expectations and of perceived position in life, but do not change their level of quality of life or can even deteriorate it. We also hypothesized that symptoms level is negatively correlated to expectations, negatively correlated to perceived position in life and not correlated or even positively correlated with quality of life.

2. Material and Methods

2.1 Study design and procedures

Data was obtained from a multicenter randomized controlled trial designed to compare the safety and efficacy of two antipsychotics (Haloperidol and Olanzapine) in two groups of patients with schizophrenia over a period of one year. The primary objective of this study was to show the superiority of Olanzapine in terms of efficacy in incompletely stabilized patients. For this purpose, a wide variety of outcomes was measured. The study was sponsored by Eli Lilly and company. The protocol was approved by an independent review board.

Adult outpatients with schizophrenia diagnosed according to DSM-IV criteria, who had been on antipsychotics for at least one year at inclusion, who had a Positive and Negative Syndrome Scale (PANSS) score over 48 and who were candidates for a switch from one antipsychotic to another were eligible. Among exclusion criteria was a hospitalization or an emergency consultation in the preceding 8 weeks. All patients signed informed consent to enter the study.

Measures of quality of life assessed with the OPS were carried out at baseline (i.e. upon change of antipsychotic) and at 6 and 12 months after baseline, while the PANSS was administered at baseline and at 1, 2, 4, 6, 8, 10 and 12 months after baseline. The severity of
the disease was assessed using the Clinical Global Impression (CGI) severity scale at baseline and at 1, 2, 4, 6, 8, 10 and 12 months after baseline.

2.2 Assessment instruments

The OPS is a two-part instrument designed to assess the acceptability of life in patients with schizophrenia, taking into account their expectations and the gap between these expectations and their perceived position in life [7]. The OPS is completed by the patient in presence of a clinician who could give explanations with regards to the content of the instrument. It is made up of two parts. In the first part, six life situations are presented. One of them is given here as example:

Mr. C is 30. He considers himself to be a street artist. He is often in pubs and cafés where he meets a lot of people. He has had numerous “girlfriends”, although no lasting relationship has been possible. Indeed he finds it difficult to accept limitations, in particular those connected with intimate relationships. He reads books on rather occult or obscure themes, and these ideas interest him. He calls this his philosophical activity. He intends to write songs. He has a sister whom he sometimes sees, but who is not particularly attentive. He lives on an adult disability allowance and owns a flat and property that his father left him, and these are managed by a guardian. He has always refused medication, since he does not feel ill. When he has a “bout” or a bad time, he is hospitalized, often against his will. At such times he takes medication which he stops taking very soon afterwards. The hospitalizations sometimes follow very close one on the other and last a long time. They are generally related to behavioral problems, incomprehensible acts, and severe agitation.
Patients have to tick boxes to state whether they find these situations “not acceptable at all”, “not really acceptable”, “fairly acceptable” or “acceptable” (rated respectively 4, 3, 2 and 1).

In the second part, the same situations are presented again and the patients are asked to tick boxes stating whether they find them “much less acceptable”, “a little less acceptable”, “a little more acceptable” or “more acceptable” than their own (rated respectively 4, 3, 2 and 1).

Three outcome scores are obtained from this instrument: the first score is computed by summing the answers from the first part of the questionnaire. This score is related to the level of expectations of the patients (the higher the score, the higher the expectations); it will be referred to as the “expectations score”. The second score is computed by summing the answers obtained from the second part of the instrument. This second score is related to the perceived position in life of patients; it will be referred to as the “position in life score” (the higher the score, the better the patients’ opinion concerning his/her own life). Finally, the third score is obtained by subtracting the first score from the second. This last score reflects the level of acceptability of the patients’ position in life relative to their expectations, in other words this score reflects the quality of life: A high score for a patient means that his perceived position in life is much higher than his expectations.

The PANSS is an instrument developed by [10] to assess positive, negative and general psychopathological symptoms. In addition to the total score, the authors used four subscales: positive symptoms, negative symptoms, general psychopathology and conceptual disorganization (the higher the scores, the worse the symptoms). The emotional distress subscale [23] was also included due to its potential relevance in this particular context.

The CGI scale is used to assess treatment response in patients with mental disorders. It is a three-item scale. The subscale “CGI severity” which is used in the present study assesses the severity of the disease using one of these items rated on a seven-point scale (1=normal to 7=extremely ill).
2.3 Statistical analyses

Baseline characteristics were summarized by descriptive statistics (means for quantitative variables and frequencies for qualitative variables). Mixed model repeated measurement analyses, with an autoregressive structure of covariance, were used to test the association between OPS or PANSS scores on the one hand and time of visit on the other hand. The same type of model was then used to explain each OPS score respectively; the explanatory variables were time, PANSS total score or sub-scores and the interaction time*PANSS.

A two-sided P-value <0.05 was taken to indicate statistical significance. Analyses were performed using SAS 8.2 [21].

3. Results

3.1 Baseline characteristics

Three hundred and six patients were included in the study, most of whom were men (70%). The mean age of the patients was 41.07 (SD =10.1). The mean score for the severity of the disease, assessed using the CGI-s, was 4.17 (SD=0.93) which corresponds to “moderately ill” patients.

3.2 Missing data

Few missing data were noted for the PANSS (6%). More missing data were found for the OPS scores (12,3% at baseline6% to 20% according to the score considered).
Patients with and without missing OPS scores were not statistically different in terms of age, gender and severity at baseline (PANSS total score and CGI severity).

3.3 Evolution in quality of life (OPS) and PANSS scores over time

Table 1 shows the evolution of PANSS scores and quality of life scores over time.

The PANSS scores decreased significantly over the period (p<0.0001), which means the patients’ symptoms improved during the observation period.

The level of expectations of the patients increased significantly over time (p=0.04) and their perceived position in life remained unchanged (p=0.86), as did their quality of life, with however a “tendency” to worsen over time (p=0.10).

3.4 Associations between OPS scores and PANSS scores

Table 2 shows the results obtained with the mixed models explaining each OPS score by time, PANSS scores and interaction time*PANSS.

In the first model, poor levels of expectations are associated with high levels of emotional distress (p=0.007), negative symptoms (p=0.01), conceptual disorganization (p=0.003) and total symptoms (p=0.03), but not with positive and general psychopathology symptoms. The more symptomatic the patients, the lower are their expectations. The interaction “time*PANSS” is significant at the 5% level for negative symptoms and total symptoms, this means that the association between these scores and a poor level of expectations is higher at the end of follow up.

In the second model, a low perceived position in life is associated with high levels of emotional distress (p=0.05), positive symptoms (p=0.04), negative symptoms (p=0.0002), conceptual disorganization (p=0.008) and total symptoms (p=0.003), but not with general psychopathology symptoms. The more symptomatic are the patients, the lower is their perceived position in life. The interaction “time*PANSS” is significant at the 5% level for
emotional distress, negative symptoms, conceptual disorganization and total symptoms, this means that the association between these scores and a low perceived position in life is higher at the end of follow up.

In the third model, quality of life is not significantly associated with symptoms.

4. Discussion To summarize our results, when engaged in a new treatment, incompletely stabilized patients with schizophrenia increase their level of expectations over time, while their perceived position in life is stable like their quality of life. When symptoms improve, level of expectations increases, perceived position in life of patients improves and quality of life is stable despite a trend toward deterioration.

Our hypotheses are thus partially verified. The main failure concerns perceived position in life that was supposed to improve with time and this is not what is observed in the present study. Our results confirm however that when symptoms improve, both expectations and perceived position in life increase leading to the stability of quality of life. Moreover in our sample we showed a trend towards decrease in quality of life which could be explained by a higher increase in expectations than in perceived position in life.

Figure 1 schematizes the possible pathways between symptoms and quality of life in patients with schizophrenia. As expected, an improvement in symptoms is associated with an increase in patients’ perceived position in life but, in parallel, with an increase in patients’ level of expectations. This phenomenon is stronger for negative symptoms as compared with positive symptoms. The combination of the increase in expectations and the increase in patients’ perceived position in life results, at best, in the stability of patients’ quality of life.

Now, how can be interpreted this pattern of relationships, in particular the association between improvement in negative symptoms and increase in patients’ level of expectations?
According to the traditional psychoanalytic theory, there exists “defense mechanisms” which “conceal from oneself internal drives or feelings that threaten to lower self-esteem or provoke anxiety” [6]. Indeed, negative symptoms could play this role here [9]. The old but still vivid concept of insight has also interesting here. There is evidence that negative symptoms are negatively correlated with insight [9, 15] and, in turn, insight could be related to expectations. To support this last hypothesis, it has been shown that insight has a complex and even paradoxical pattern of relationships with subjective outcomes like hope and self-esteem [12]. In particular, patients with an inner experience of stigma or with a low level of social support are at a particular risk when their level of insight increases [12, 17]. Indeed, concerning stigma, it is possible that once symptoms are improving, the patient realizes that his or her place in the society is not what it should be and hence raises his or her level of expectations. More generally, following the phenomenological tradition, even if symptoms improve and \textit{because} symptoms have improved, a patient can realize that he or she will never live anymore in a world where there is an “ease and smooth flow of normal experience”, where meaning is given a priori, without any cognitive efforts [2, 26]. And this is likely to be no more acceptable. Finally, the phenomenon we are trying to explain here is perhaps not specific to schizophrenia. A famous utilitarian philosopher like John Stuart Mill clearly stated that satisfaction, lucidity and goal in life have a complex pattern of relationships: « better to be Socrates dissatisfied than a fool satisfied » [14]. To stay in the field of economy, several studies have shown that average self-declared happiness does not increase in time with average income per capita, this is called the Easterlin paradox and it remains a controversial and vividly debated topic [5].

In practice and to keep it simple, measuring patients’ expectations from life would help caregivers ensure that patient’s new goals are not inappropriate, in order to avoid a sense
of inadequacy in these patients, leading to a decrease in relative acceptability of life. Action of this sort could even lead to a decrease in suicide rates among patients with schizophrenia, as it has been shown that high aspirations are associated with suicidality in this population [19].

One of the advantages of this study is the use of a new approach in the assessment of quality of life outcomes in patients with schizophrenia, showing the importance of taking expectations distinctly into account when measuring quality of life, which is not at present the rule in most existing instruments [4]. Moreover, the power of this study lies in its large sample size and longitudinal design.

Certain limitations must be pointed out. In the OPS instrument, the patients are asked to say how they perceive other patients’ lives and to position themselves in relation to these lives. This task requires a good level of cognition. Therefore the validity of the answers given by patients with schizophrenia can be questioned, since schizophrenia is known to be an illness that affects perception of reality and cognitive abilities. However, the OPS instrument is rated in presence of a clinician and it was administered in this study to patients without hospitalization or emergency consultation in the last 8 weeks, which is in favor of reliable answers. This is confirmed by the acceptable psychometric reliability of the OPS scores in the present sample [7]. Finally, our results might not generalize to patients with schizophrenia as a whole because of the selection of a specific population through the inclusion criteria. Another limitations stands in the absence of reliable measurement of depression, which could have play the role of a mediator or a moderator in the relationships that have emerged.

It is clearly recognized that treatments improve patients’ health state and quality of life as measured by classic questionnaires [8]. In addition, quality of life is negatively correlated to severity of positive, negative, depressive and anxiety symptoms, with a possible greater impact of depression and anxiety [1, 11, 16, 24]. However, the pathways between quality of life and symptoms are still not clear. In the present study, the OPS instrument measures a
construct related to Calmans’ definition of quality of life as the gap between expectations and achievements. In this sense of the concept, when patients with schizophrenia are treated, their quality of life remains stable. Caregivers should be aware of this result, especially when classic indicators seem to be improving. Including disappointment of confrontations with reality in therapeutic strategies could help patients with schizophrenia coping with the increase in their level of expectations.
References

Figure 1  Patterns of relationships between symptoms and quality of life. “Perceived position in life” is related to how the patient perceives his/her life in terms of acceptability with regard to six typical life situations of patients with schizophrenia. “Quality of life” is related to the gap that exists between the way a patient considers his/her life and the way he/she would like it to be.
**Table 1** Changes in OPS and PANSS scores over time. A high OPS “expectation score” corresponds to a high level of expectations. A high OPS “position in life” score corresponds to a high perceived position in life. A high OPS “quality of life” score corresponds to a high level of quality of life: perceived position in life is much higher than expectations.

<table>
<thead>
<tr>
<th></th>
<th>Visit 2 (baseline)</th>
<th>Visit 6 (6 months)</th>
<th>Visit 9 (12 months)</th>
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<tr>
<td></td>
<td>mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
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<tr>
<td>OPS expectations score</td>
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<td>3.4</td>
<td>11.8</td>
<td>3.9</td>
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<tr>
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<td>13.92</td>
<td>3.2</td>
<td>13.7</td>
<td>3.8</td>
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<tr>
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<td>2.16</td>
<td>3.7</td>
<td>1.89</td>
<td>3.6</td>
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<td>79.19</td>
<td>16.5</td>
<td>60.70</td>
<td>15.4</td>
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<tr>
<td>PANSS subscales</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Positive symptoms</td>
<td>16.50</td>
<td>4.9</td>
<td>12.12</td>
<td>3.8</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>23.05</td>
<td>5.7</td>
<td>18.05</td>
<td>5.1</td>
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<td>39.64</td>
<td>9.7</td>
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<tr>
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<td>7.28</td>
<td>2.2</td>
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<tr>
<td>Emotional distress</td>
<td>27.68</td>
<td>6.6</td>
<td>21.8</td>
<td>6.3</td>
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</table>
**Table 2** Associations (regression coefficient) between each OPS score (dependent variable) and each PANSS score (predictor). Mixed model for repeated measurements with “time” and interaction “time*PANSS score” as supplementary predictors. “NS” and “S” stand respectively for “Non Significant” and “Significant” (5% level).

<table>
<thead>
<tr>
<th>Predictors (PANSS)</th>
<th>Dependent variable</th>
<th>OPS Expectation</th>
<th>OPS position in life</th>
<th>OPS Quality of life</th>
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</thead>
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<tr>
<td>Total Symptoms</td>
<td>OPS Expectation</td>
<td>-0.02 (p=0.03)</td>
<td>-0.03 (p=0.003)</td>
<td>-0.005 (p=0.69)</td>
</tr>
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<td>Time</td>
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<td>S (&lt;0)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Interaction</td>
<td>NS</td>
<td>S (&lt;0)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>Time</td>
<td>-0.03 (p=0.54)</td>
<td>-0.09 (p=0.04)</td>
<td>-0.04 (p=0.31)</td>
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<tr>
<td></td>
<td>Interaction</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>Time</td>
<td>-0.09 (p=0.01)</td>
<td>-0.13 (p=0.0002)</td>
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<td>S (&lt;0)</td>
<td>S (&lt;0)</td>
<td>NS</td>
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<tr>
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<td>Time</td>
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<td>0.006 (p=0.77)</td>
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<td></td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Conceptual disorganization</td>
<td>Time</td>
<td>-0.24 (p=0.003)</td>
<td>-0.22 (p=0.008)</td>
<td>0.0005 (p=0.88)</td>
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<td>NS</td>
<td>NS</td>
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<td>Time</td>
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<td>-0.06 (p=0.05)</td>
<td>0.03 (p=0.26)</td>
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<td></td>
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<td>NS</td>
<td>S (&lt;0)</td>
<td>NS</td>
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