BJPsych The British Journal of Psychiatry (2008) 193, 203–209. doi: 10.1192/bjp.bp.108.049718

Duration of untreated psychosis and social function: 1-year follow-up study of first-episode schizophrenia

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Background
In first-episode schizophrenia, longer duration of untreated psychosis (DUP) predicts poorer outcomes.

Aims
To address whether the relationship between DUP and outcome is a direct causal one or the result of association between symptoms and/or cognitive functioning and social functioning at the same time point.

Method
Symptoms, social function and cognitive function were assessed in 98 patients with first-episode schizphrenia at presentation and 1 year later.

Results
There was no significant clinical difference between participants with short and long DUP at presentation. Linear regression analyses revealed that longer DUP significantly predicted more severe positive and negative symptoms and poorer social function at 1 year, independent of scores at presentation. Path analyses revealed independent direct relationships between DUP and social function, core negative symptoms and positive symptoms. There was no significant association between DUP and cognition.

Conclusions
Longer DUP predicts poor social function independently of symptoms. The findings underline the importance of taking account of the phenomenological overlap between measures of negative symptoms and social function when investigating the effects of DUP.

Declaration of interest
None. Funding detailed in Acknowledgements.

Evidence from early studies of first-episode schizophrenia suggested that a longer period of unchecked, untreated illness was associated with a poorer prognosis.[1–3] This association has been supported in some further studies,[4–9] but not all.[10–12] However, two systematic reviews concluded that whereas a longer duration of untreated psychosis (DUP) is associated with a worse response to antipsychotic medication in the first year of treatment in terms of positive and negative symptoms, the relationship with social function is less consistent.[13,14] There are limited data on the relationship between DUP and cognitive function at baseline or after a period of treatment with antipsychotic medication, but few of the relevant studies have found any association.[14,15]

Several studies indicate that social functioning in people with psychosis is correlated with a number of concomitant factors, including positive and negative symptoms, disorganisation syndrome and cognitive functioning.[16–18] Since all of these aspects of functioning have been purported to be worse in people with a longer DUP, this raises the question of whether the relationship between DUP and outcome is a direct causal one or rather the result of an association between symptoms and/or cognitive functioning and social functioning at the same time point – a mediated relationship. As DUP is potentially a prognostic factor open to intervention, previous work has tried to determine whether its association with poorer outcome represents a causal relationship or whether it is an epiphenomenon, with a common underlying factor, such as poor premorbid function or insidious onset of illness.[12,19] This study explores a related aspect: which outcome factors are directly linked with DUP. Greater understanding of this might help to explain the result of any intervention aimed at reducing DUP.

In the West London First Episode Schizophrenia Study we investigated prospectively a sample of people presenting for the first time with schizophrenia and assessed the influence of DUP on 1-year outcome. Measures of outcome were positive, negative and disorganisation syndromes, social function and cognition. Based on previous research, our hypothesis was that longer DUP would predict increased symptoms and worse social functioning but not cognitive functioning at follow-up. We also predicted that the effect of DUP on social functioning at follow-up would be mediated via symptoms at the same time point and that there would be no direct relationship between DUP and social function at follow-up once this indirect relationship was taken into account.

Method

Sample

Individuals recruited into the prospective West London First Episode Schizophrenia Study (n=135) received clinical and neuropsychological assessments at initial presentation.[20] Inclusion criteria were that an individual was experiencing his or her first episode of psychosis, had been prescribed antipsychotic medication for less than 12 weeks, fulfilled DSM–IV criteria for schizophrenia (n=97) or schizoaffective disorder (n=1),[21] was aged 16–55 years and had a command of English sufficient to participate in the range of assessments.

Assessments

Duration of untreated psychosis and of untreated illness

The dates of onset of prodromal and psychotic symptoms were elicited as previously reported,[19] with sources of information including patient interview, clinical case-notes and questioning of the relatives and carers. Duration of untreated psychosis was

calculated as the time from onset of psychotic symptoms to first treatment with antipsychotic medication. Duration of untreated illness (DUI) was calculated as DUP plus any prodromal period.

Participants were assessed at the time of their first presentation to psychiatric services, and subsequently at 1-year follow-up, using the same measures, described below.

Mental state

The participants' mental state was assessed with the Scale for Assessment of Positive Symptoms (SAPS) and the Scale for Assessment of Negative Symptoms (SANS).[22] Three symptom-derived syndrome scores were derived:[23,24] positive syndrome (SAPS hallucinations and delusions), disorganisation syndrome (SAPS bizarre behaviour and positive formal thought disorder) and negative syndrome (all SANS sub-scales), as well as a score for the 'core' negative symptoms of flat affect and poverty of speech (SANS sub-scale scores for affective flattening and alogia).[25,26]

Cognition

At initial assessment, premorbid IQ was estimated using the National Adult Reading Test (revised version).[27] Measures of neuropsychological function were obtained at both baseline and follow-up using a 4-sub-test, short form of the Wechsler Adult Intelligence Scale – Revised (WAIS–R) and the Cambridge Automated Neuropsychological Test Battery (CANTAB).[28,29] From the CANTAB, executive function (Tower of London planning, attentional set shifting and spatial working memory) and memory (spatial span and pattern recognition memory) tasks were employed.

Social function

Social function and re-integration into the community were assessed using the Social Function Scale (SFS). This is a 79-item, self-report scale, which Birchwood *et al* showed to be a reliable, valid and sensitive measure of social functioning in individuals with schizophrenia.[30] Individuals rate their abilities in seven areas: activation–engagement, interpersonal communication, frequency of activities of daily living, competence at activities of daily living, participation in social activities, participation in recreational activities, and employment/occupational activity.

Statistical analysis

Data were initially analysed using SPSS version 14 for Windows. To examine group differences, *t*-tests were used for continuous data and chi-squared tests for categorical data. Linear regressions were used to examine effect of DUP on 1-year outcome. Mplus (version 5; www.statmodel.com) path analysis was used to investigate the relationship between DUP and the follow-up scores for the positive syndrome, negative syndrome and social function scores.

Results

Of the 135 patients who received clinical and neuropsychological assessments at initial presentation, 98 (73%) were re-assessed approximately 1 year later (median follow-up period 383 days). When the group of participants lost to follow-up were compared with those who were assessed at follow-up on the demographic, clinical and IQ measures at initial presentation, there was no significant difference on any measure (age at onset, t_{133}=0.15; age at testing, t_{133}=0.58; negative syndrome, t_{133}=1.53; positive syndrome, t_{133}=0.97; disorganisation syndrome, t_{133}=0.92; DUP, t_{133}=1.47; National Adult Reading Test premorbid IQ, t_{122}=0.58; WAIS–R current IQ, t_{124}=1.32; medication, χ^2=0.47; gender, χ^2=0.53; all NS).

For the 98 participants re-assessed at 1 year the median value for DUP was 20 weeks and the mean was 52.5 weeks (s.d.=82.6). In 13 individuals no accurate estimate of DUI was possible, and data for these cases were therefore excluded from any analyses relating to DUI. The median DUI for the remaining 85 patients was 104 weeks and the mean was 188.9 (s.d.=248.1). For analysis using parametric statistics, both DUP and DUI scores were $\log_{10}$ transformed because of positive data skewness. Table 1 shows the correlations between both $\log_{10}$ DUP and $\log_{10}$ DUI for the clinical outcome measures at follow-up. Given the lack of significant correlations between DUI and syndrome scores and also overall social function, DUI was not included in further analyses.

In the initial exploration of the data, the sample was dichotomised into those with a short or long DUP, using a median split,[12,31] although later analyses used DUP as a continuous measure. These two groups did not significantly differ on measures which, based on *a priori* expectations from previously published studies, could be considered a significant predictor of outcome (age at onset, t_{96}=0.62; premorbid IQ, t_{90}=0.44; gender, χ^2=0.65; follow-up period, t_{96}=0.60; all NS).

There was no significant difference between short and long DUP groups on SFS total score, positive, negative and disorganisation syndromes scores and core negative symptoms at initial presentation (Table 2). At 1 year significant differences were found for negative and positive syndrome scores and total SFS score (Table 2). When the SFS sub-scales were examined there were significant differences for activation–engagement, frequency of activities of daily living, participation in social activities and employment/occupation activity.

To evaluate the extent to which DUP influenced these measures at 1 year, a series of stepped linear regressions were performed. Significant correlations were found between initial and 1-year scores for positive syndrome (r=0.33, P=0.001), negative syndrome (r=0.19, P=0.064) and SFS total score (r=0.40, $P<0.001$). Thus, for each outcome variable, the score at initial presentation was entered in the first step to control for the effect of baseline function on outcome, and the score at 1 year was entered as the second step. This approach allows any differences in follow-up scores to be confidently ascribed to the effect of DUP on outcome, independent of functioning at first

Table 1 Pearson correlation coefficients between $\log_{10}$ duration of untreated illness, $\log_{10}$ duration of untreated psychosis, and symptom syndrome scores and social function assessed at 1-year follow-up

	$\log_{10}$ DUP	$\log_{10}$ DUI
Negative syndrome	0.260**	0.114
Positive syndrome	0.284**	0.109
Disorganisation syndrome	0.056	−0.068
Social Function Scale		
Total score	−0.312**	−0.166
Activation–engagement	−0.335**	−0.197
Interpersonal communication	−0.180*	−0.126
Frequency of activities of daily living	−0.218*	−0.042
Competence at activities of daily living	−0.110	0.055
Participation in recreational activities	−0.113	−0.036
Participation in social activities	−0.256*	−0.284**
Employment/occupation activity	−0.301**	−0.186

DUI, duration of untreated illness; DUP, duration of untreated psychosis.
*$P<0.05$, **$P<0.01$.

Table 2 Clinical and key outcome variables at baseline and follow-up

Variable	Initial presentation			1-year follow-up		
	DUP ⩽20 weeks	DUP >20 weeks	Statistical test	DUP ⩽20 weeks	DUP >20 weeks	Statistical test
Participants, *n*	52	46				
Follow-up period, days: mean (s.d.)				518 (338)	564 (426)	
DUP, weeks: mean (s.d.)	7.3 (5.9)	106.7 (106.4)				
Type of medication, *n*						
1. Drug free	3	7		8	5	
2. First-generation antipsychotic	27	18	(excluding group 4)	19	16	(excluding group 4)
3. Second-generation antipsychotic	21	18	χ^2=2.97, d.f.=2, NS	25	25	χ^2=0.58, d.f.=2, NS
4. Combined first- and second-generation antipsychotics	1	3		0	0	
Negative syndrome score: mean (s.d.)	0.41 (0.27)	0.39 (0.27)	t_{96}=0.33, NS, d=0.07	0.21 (0.22)	0.32 (0.23)	t_{94}=2.31, *P*=0.023, d=0.48
Positive syndrome score: mean (s.d.)	0.70 (0.26)	0.66 (0.27)	t_{96}=0.73, NS, d=0.15	0.17 (0.25)	0.29 (0.32)	t_{94}=2.04, *P*=0.044, d=0.41
Disorganisation syndrome score: mean (s.d.)	0.43 (0.29)	0.35 (0.28)	t_{96}=1.25, NS, d=0.28	0.06 (0.15)	0.06 (0.13)	t_{94}=0.001, NS, d=0.0
Overall SFS score: mean (s.d.)	111.76 (13.98)	108.10 (11.73)	t_{86}=1.32, NS, d=0.28	115.2 (8.9)	108.2 (12.7)	t_{91}=3.07, *P*=0.003, d=0.62
SFS sub-scale (scaled) score: mean (s.d.)						
Activation–engagement	99.16 (13.30)	100.49 (14.40)	t_{86}=0.45, NS, d=0.09	107.74 (12.50)	99.78 (11.67)	t_{93}=3.20, *P*=0.002, d=0.62
Interpersonal communication	112.89 (23.98)	110.02 (22.08)	t_{86}=0.58, NS, d=0.12	120.12 (18.65)	114.20 (21.18)	t_{93}= 1.44, NS, d=0.30
Frequency of activities of daily living	114.65 (19.21)	108.24 (21.54)	t_{86}=1.47, NS, d=0.31	116.30 (14.42)	108.99 (18.36)	t_{93}= 2.17, *P*=0.033, d=0.44
Competence at activities of daily living	115.75 (17.03)	113.81 (11.97)	t_{86}=0.61, NS, d=0.13	116.01 (11.92)	114.06 (13.67)	t_{93}= 0.75, NS, d=0.15
Participation in recreational activities	113.14 (20.47)	108.62 (18.63)	t_{86}=1.08, NS, d=0.23	114.55 (17.04)	109.39 (19.97)	t_{93}= 1.36, NS, d=0.28
Participation in social activities	117.61 (17.67)	110.26 (17.04)	t_{86}=1.97, *P*=0.052, d=0.42	120.36 (11.77)	110.89 (20.72)	t_{93}= 2.77, *P*=0.007, d=0.55
Employment/occupation activity	110.92 (15.31)	105.23 (13.73)	t_{86}=1.82, *P*=0.072, d=0.39	110.91 (11.78)	101.74 (15.32)	t_{93}=3.28, *P*=0.001, d=0.64

DUP, duration of untreated psychosis; NS, not significant; SFS, Social Function Scale.

presentation. Duration of untreated psychosis was a significant predictor of the outcome in each case (positive syndrome: *F* change=7.06, *P*=0.009, r^2=0.06; negative syndrome: *F* change=9.39, *P*=0.003, r^2=0.09; SFS overall score: *F* change=7.36, *P*=0.008, r^2=0.07).

Between 90 and 95 participants completed each neuropsychological test. Independent samples *t*-tests for current IQ and all continuous cognitive variables (spatial span, spatial working memory strategy and error scores, pattern recognition memory and Tower of London perfect solutions) revealed that there was no significant difference between the short and long DUP groups on any of these measures at either baseline or follow-up (range of *t*-test values at baseline 0.15–1.70; range at follow-up 0.25–1.34). Chi-squared analysis confirmed that there was no significant interaction between DUP and passing or failing the attentional set-shifting task at initial presentation (χ^2=0.82, NS) or follow up (χ^2=1.05, NS).

Path analysis

To determine whether the relationship between DUP and social function at 1-year follow-up was mediated by 1-year positive and/or negative syndrome scores, a path analysis was performed (model 1). We repeated the analysis substituting the core negative symptoms, SANS affective flattening and alogia for the negative syndrome score derived from the whole SANS scale (model 2). The core negative symptoms scores are not anchored with items of self-care and occupational and social functioning, which may reflect outcome instead of actual symptoms.[32] This allowed delineation of the effect of social relationships and recreational activities potentially covered by both the SFS and SANS (e.g. ability to enjoy activities and relationship with friends/peers).

Although DUP was log-transformed to give an approximately normal distribution, it was not possible to transform the other variables (negative syndrome, positive syndrome and core negative symptoms) into the normal distribution, therefore we used bootstrap confidence intervals to allow for this.

Model 1 (incorporating the negative syndrome)

Results showed that a large component (39% of the explained variance in social function) of the effect was a direct effect of DUP on social function, although this did not achieve statistical significance (*P*=0.11). The DUP had a large and significant effect on positive syndrome score (*P*=0.002) but the positive syndrome score had no effect on social function score (*P*=0.30). Thus, the pathway from DUP to social function via positive syndrome was not significant and only accounted for 2% of the explained variance (*r*=−0.03; *P*=0.35). Note that the effect size via an indirect pathway is obtained by multiplying the effect sizes of each component part of that pathway. For example, the effect size of DUP on social function via positive syndrome is −0.03 (0.29 × −0.11). Duration of untreated psychosis had a significant effect on the negative syndrome score (*P*=0.004) and negative syndrome score also had a significant effect on social function score (*P*<0.0001). This resulted in the pathway from DUP to social function via negative syndrome being significant, accounting for 59% of the explained variance in social function (*r*=−0.16, *P*=0.02) (Fig. 1).

There is strong evidence that these pathways collectively explain a significant amount of the variation in social functioning (χ^2(6)=74.03, *P*<0.0001), and the goodness-of-fit chi-squared parameter suggests that there is only a modest amount of remaining variation to be explained (χ^2(1)=5.39, *P*=0.02). However, the root mean square error of approximation (RMSEA) statistic (0.218, 90% CI 0.069–0.413) suggests that a modest proportion of the variance remains unexplained by this model, and therefore other variables that are not included in the model may also affect social functioning at follow-up.

Model 2 (incorporating core negative symptoms)

A large, significant component of the effect was direct from DUP to social function score, accounting for 78% of the explained variance in social function in this model (*r*=–0.19, *P*=0.04). Duration of untreated psychosis had a large and significant effect

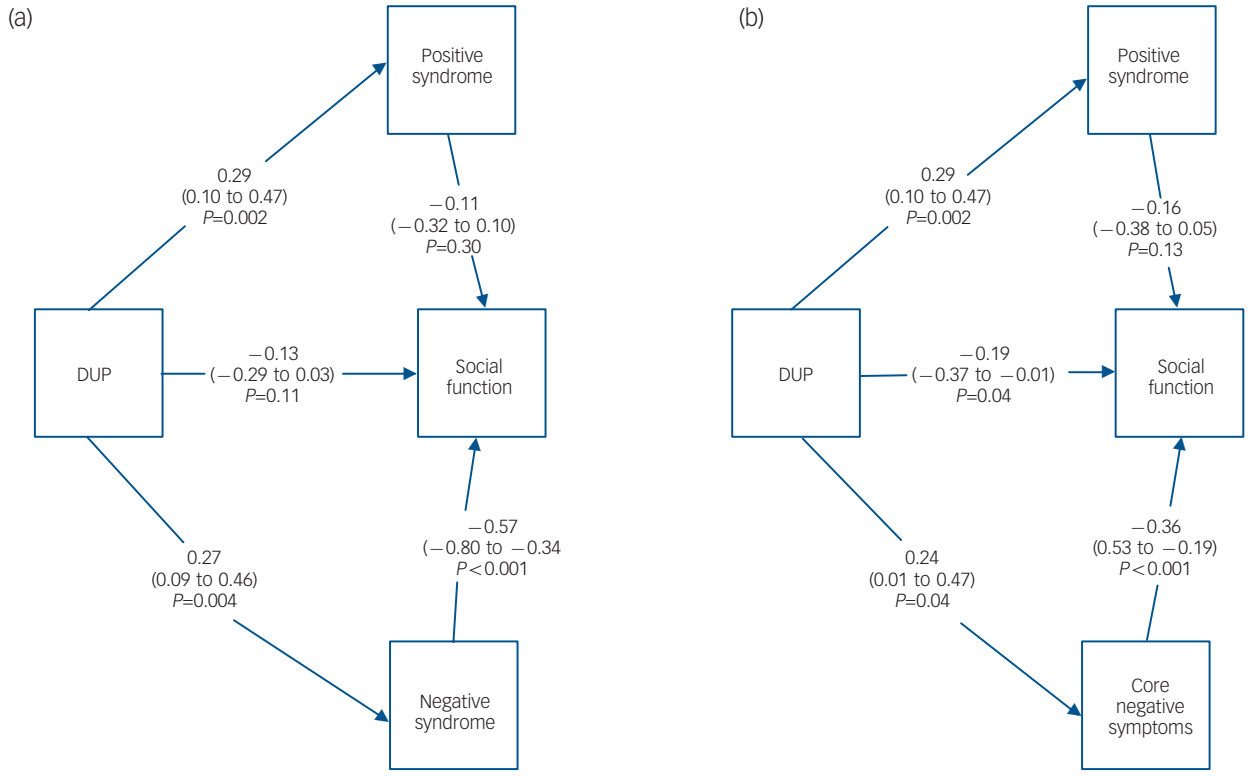

Fig. 1 Model 1 (a) showing results from path analysis incorporating negative syndrome, with bootstrap correction for non-normality. Model 2 (b) showing results from path analysis incorporating core negative symptoms, with bootstrap correction for non-normality. For both models, the results show the standardised regression coefficients (equivalent to correlation coefficients) for the different arms, with associated 95% confidence intervals and *P*-values. DUP, duration of untreated psychosis.

on positive syndrome score (P=0.002), but the effect of positive syndrome score on social function score was not significant (P=0.13). Thus, the pathway from DUP to social function via positive syndrome was not significant and accounted for only 5% of the explained variance (r=−0.05, P=0.19). Duration of untreated psychosis had a significant effect on core negative symptom score (P=0.04) and core negative symptom score also had a significant effect on social function score (P<0.0001). This resulted in the pathway from DUP to social function via core negative symptoms accounting for 17% of the explained variance, although this failed to reach significance (r=−0.09, P=0.10). Again, there is strong evidence that these pathways collectively explain a significant amount of the variation in social functioning ($\chi^2(6)$=51.70, P<0.0001), and the goodness-of-fit chi-squared parameter suggests that there is no appreciable remaining variation to be explained ($\chi^2(1)$=2.36, P=0.12). However, once again the RMSEA statistic (0.122, 90% CI 0.000–0.333) suggests that other variables may also affect social functioning at follow-up.

Discussion

We found that a longer DUP was related to a greater severity of positive and negative symptoms and poorer social function 1 year after the start of antipsychotic treatment, and that this was independent of age at onset of psychosis and the severity of symptoms and social function at initial presentation. When we used path analysis to assess the interdependence of these relationships we found that DUP was directly and independently related to residual positive and negative symptoms. However, the effect of DUP on social function was more complex. Although this was independent of the DUP effect on positive symptoms, the possibility of a mediating effect of negative symptoms on social function depended on whether a narrow or broad concept of the negative syndrome was employed.

Duration of untreated psychosis and symptoms

We failed to find any significant association between longer DUP and more severe positive and negative symptoms on first admission.[19] Similar findings have been reported,[33] although several previous studies of first-episode psychosis have found such an association.[4,33,34] One possible explanation for the failure to observe such a relationship at first episode is that for most people in the sample the presentation to psychiatric services is likely to have been prompted by reaching a threshold level of severity of symptoms, thus obscuring any relationship with DUP.

Studies of the relationship between DUP and symptoms following a period of treatment have also yielded inconsistent findings. Whereas most longitudinal first-episode studies have found that a longer DUP predicts more severe and enduring positive symptoms,[6–8] a positive association between DUP and negative symptoms has been found in some studies,[7,36–38] but not in others.[8,10,39] The variability in findings may partly reflect differences in the relationship between DUP and negative symptoms between subgroups of patients with first-episode disorder.[40] Another potential explanation concerns the measures used to assess the negative syndrome. Thus, in this study when we used a negative syndrome score derived from all sub-scales of the

SANS, we found a stronger relationship with DUP than when we used only core negative symptoms in the analysis.

Although Addington *et al* failed to find an association between DUP and negative symptoms, they speculated that when such an association is reported it may reflect either that negative symptoms pre-date onset and hinder help-seeking or that longer DUP itself leads to enduring negative symptoms.[8] Against the former explanation of our results is that DUP remained a significant predictor of follow-up symptom scores when controlling for the influence of the respective baseline symptom scores, suggesting that DUP is influencing outcome over the initial year of treatment. Supporting this conclusion is the finding of an association between DUP and enduring negative symptoms by Edwards *et al* even after they had controlled for premorbid function.[41]

Duration of untreated psychosis and social function

As with negative symptoms, the evidence for a relationship between longer DUP and indices of poorer social and occupational functioning following treatment is inconsistent.[14,42] Again, this may reflect the different measures employed. In our study, social function and re-integration into the community were assessed using the SFS, which was specifically designed to evaluate social function in people with schizophrenia.[30] We found that a longer DUP was associated with poorer overall social function at follow-up, which was largely a reflection of significantly poorer social engagement and a lower frequency of activities of daily living, as well as less participation in social activities and lack of employment or occupation. When we examined whether poorer social function at 1-year follow-up was mediated by the effects of DUP on positive and negative symptoms, using a path analysis, we found that the relationship between DUP and social function was unambiguously independent of positive symptoms. The relationship between DUP, negative symptoms and social function, on the other hand, depended on whether SANS general or core negative symptoms were used in the analysis. When the full range of SANS negative symptoms was used, the relationship between longer DUP and poor social function was largely mediated via the negative syndrome, reflecting 59% of the variance. When the analysis was repeated using only core negative symptoms, the relationship between longer DUP and poor social function was not mediated via the negative syndrome and instead, a major part of the variance (78%) was explained by the direct effect of DUP on social function.

The measure of core negative symptoms adopted in this study assessed the severity of flatness of affect and poverty of speech using the alogia and affective flattening sub-scales of the SANS.[25,26] The remaining SANS sub-scale measures of avolition, anhedonia and attentional impairment were excluded because they contain items assessing self-care and occupational and social functioning, which arguably reflect social function rather than symptoms intrinsic to the disorder.[32] This method therefore allowed a delineation of the effect of DUP on social relationships and recreational activities potentially covered by both the SFS and SANS scales. The difference in our findings when narrow and broad concepts of the negative syndrome were used probably reflects the phenomenological overlap between the two scales.[32,43] What is clearly demonstrated by these two contrasting models is how fundamentally important the conceptualisation of these overlapping elements is when analysing and interpreting the relationship between DUP and outcome.

Duration of untreated psychosis and cognition

We found no evidence of any significant difference in global IQ or performance on a range of cognitive tests between those with short and long DUP at either initial presentation or follow-up. We have previously reported that in the same baseline sample, assessed at first presentation, longer DUP was related to impaired performance on the attentional set-shifting task but to no other neuropsychological measure.[44] The disparity between these results may reflect differences in the definition used for success on the attentional set-shifting task. In the study reported here, participants were dichotomised into those passing and failing the task, and this required completion of all nine stages. In the earlier study we examined the stage reached, and, of the participants who did not reach stage nine, it is possible that, on average, those with a short DUP progressed to a later stage than those with a longer duration.[44] However, the results of both studies suggest that DUP does not broadly affect cognition. Further, the current findings are consistent with other longitudinal first-episode studies which have failed to find a relationship between DUP and cognitive function.[8,45–47] Although cognitive impairment may be a risk factor for the onset of psychosis,[48] our findings suggest that cognitive function does not mediate the relationship between DUP and the outcomes we examined.

Implications of the findings

One hypothesis put forward to explain the association between longer DUP and a worse outcome in terms of psychotic symptoms is that there is an active morbid process with unchecked psychosis, which may be slowed or attenuated by treatment with antipsychotic medication.[49] Keshavan *et al* reported that longer DUP is associated with a decrease in superior temporal gyral volume,[50] and more recently Lappin *et al* found that temporal grey-matter reductions were more marked in patients with long DUP.[51] These findings may reflect a progressive pathological process that is active prior to treatment,[52] and if antipsychotic treatment delays or prevents the structural brain changes associated with psychosis,[53] increased neuronal damage would be associated with greater DUP. Although the exact underlying mechanism remains to be determined, it is plausible that this neuronal damage impedes treatment response and, specifically, symptom reduction with antipsychotic medication, resulting in the greater residual positive and negative symptoms found in patients with longer DUP both in this study and elsewhere.[6,7] However, the direct effect of DUP on social function, revealed by specifically excluding negative symptoms that partly reflect social function, cannot be so easily explained as a direct result of neuronal damage, since social function is arguably even more removed than clinical symptoms from the pathophysiological basis of the illness. Rather, this finding suggests that important factors other than symptoms mediate the effect of DUP on social function, with social perception and social knowledge being likely candidates.[54,55]

In summary, our findings suggest that longer DUP has predictive value for poorer clinical and social outcome in schizophrenia in respect of persistent symptoms and social re-integration that is independent of age, age at onset of psychosis and the clinical ratings of these outcome domains at first presentation to services. They also have implications for the interpretation of the results of previous first-episode studies reporting the relationship between DUP, and the level of social function and severity of negative symptoms following a period of treatment. Certain elements relevant to social function, such as self-care, work function and interpersonal relationships, are common to measures of these two domains, and thus there is the potential for confounding of their association with DUP. However, our results provide evidence for a direct relationship between DUP and social function when this overlap is addressed.

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First received 23 Jan 2007, final revision 17 Jan 2008, accepted 25 Feb 2008

Acknowledgements

The study was supported by a Wellcome Trust programme grant (064607). We acknowledge the help of Mrs I. Harrison, Dr B. Puri and Dr M. Chapman with data collection.

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psychiatry in music

Emotion in Beethoven and his music

François Mai

Beethoven was the first of the romantic period composers who dominated classical music during the 19th century. He himself was a passionate man who carried his feelings on his sleeve. He had episodes of depression accompanied by suicidal ideas, and rarer episodes of elation with flights of ideas. The latter are reflected in some of his letters. He had a low frustration tolerance and at times would become so angry that he would come to blows with others such as his brother Carl, or he would throw objects at his servants. Although he never married, he had several affairs, including one with a married woman who has come to be known to posterity as 'the Unknown Beloved'. To her he wrote three love letters that are filled with affection and feeling. He much enjoyed wine and this resulted in hepatic cirrhosis that caused his premature death at the age of 56.

This moodiness is reflected in his music. The 'Marches Funébres' of his Third Symphony (*Eroica*) and the Piano Sonata, op. 26, no. 12, are poignant and powerful portrayals of grief and bereavement. The final movement of the String Quartet, no. 6, op. 18 (*La Malinconia*) has sudden and alternating changes of tempo and rhythm that depict, in musical terms, the mood changes that occur in bipolar disorder. The pace and fortissimo dynamics of both his Rondo a Capriccio for piano, op. 129 and the storm movement of his Sixth Symphony (*Pastoral Symphony*) beautifully (or perhaps one should also say fearfully) display anger and agitation.

Beethoven also displayed positive emotions in his music. The prime example is his rendering of Schiller's poem *Ode to Joy* in his Ninth Symphony (*Choral Symphony*), where the lyrical exaltation of peace and of our common brotherhood and humanity are beautifully and powerfully rendered in musical terms. Tenderness and love shine forth in the third movement of the Piano Sonata, op. 90, no. 27, and in the well-known Bagatelle, *Für Elise*. During the last eight years of his life Beethoven was almost totally deaf yet during this time he composed some of his most complex and profoundly spiritual music. His deafness forced him to turn inward for inspiration, and his music during this final period of his compositional career reflects the inner peace he had achieved despite the outward turmoil of his life. The late string quartets are a sublime portrayal of this mental attitude.

Beethoven is considered to be one of the greatest composers of all time. During most of his life he had many medical and psychological problems. He may have suffered from bipolar disorder. D. Jablow Hershman and Dr Julian Lieb in their book *Manic Depression and Creativity* have argued quite convincingly that Beethoven was manic depressive. His medical problems included progressive deafness that began in his late twenties, chronic alcohol dependency causing cirrhosis of the liver, lead poisoning and a chronic gastro-intestinal condition (likely irritable bowel syndrome complicated by laxative misuse). Because of the strength of his personality and knowledge of the power of his message, he was able to rise above these ailments. As he himself on occasion admitted, composing for him was therapeutic. His deafness forced him to withdraw from teaching, performing and conducting, hence all his energies were focused on composition. His passionate nature is reflected in the passions of his music. We are all the beneficiaries.

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The British Journal of Psychiatry (2008) 193, 209. doi: 10.1192/bjp.193.3.209

Duration of untreated psychosis and social function: 1-year follow-up study of first-episode schizophrenia

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BJP 2008, 193:203-209.
Access the most recent version at DOI: 10.1192/bjp.bp.108.049718