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ORIGINAL ARTICLE

Hippocampal volume change relates to clinical outcome in childhood-onset schizophrenia

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Background. Fixed hippocampal volume reductions and shape abnormalities are established findings in schizophrenia, but the relationship between hippocampal volume change and clinical outcome has been relatively unexplored in schizophrenia and other psychotic disorders. In light of recent findings correlating hippocampal volume change and clinical outcome in first-episode psychotic adults, we hypothesized that fewer decreases in hippocampal volume would be associated with better functional outcome and fewer psychotic symptoms in our rare and chronically ill population of childhood-onset schizophrenia (COS) patients.

Method. We prospectively obtained 114 structural brain magnetic resonance images (MRIs) from 27 COS subjects, each with three or more scans between the ages of 10 and 30 years. Change in hippocampal volume, measured by fit slope and percentage change, was regressed against clinical ratings (Children's Global Assessment Scale, Scale for the Assessment of Positive Symptoms, Scale for the Assessment of Negative Symptoms) at last scan (controlling for sex, time between scans and total intracranial volume).

Results. Fewer negative symptoms were associated with less hippocampal volume decrease (fit slope: $p = 0.0003$, and percentage change: $p = 0.005$) while positive symptoms were not related to hippocampal change. There was also a relationship between improved clinical global functioning and maintained hippocampal volumes (fit slope: $p = 0.025$, and percentage change: $p = 0.043$).

Conclusions. These results suggest that abnormal hippocampal development in schizophrenia can be linked to global functioning and negative symptoms. The hippocampus can be considered a potential treatment target for future therapies.

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Key words: Childhood-onset schizophrenia, hippocampus, magnetic resonance imaging, negative symptoms, psychosis.

Introduction

Childhood-onset schizophrenia (COS), defined by an onset of psychosis before the age of 13 years, is a rare and devastating form of the disorder clinically and neurobiologically resembling adult schizophrenia – but with a chronic, non-episodic course and poorer outcome (Nicolson & Rapoport, 1999). Our prospective study on COS has been in progress at the National Institutes of Health since 1990.

There are many known structural brain abnormalities in schizophrenia, including increased ventricular size, reduced gray matter (GM) volume in frontal and temporal regions, reduced brain size (Wright *et al.* 2000; Honea *et al.* 2005), abnormal hippocampal shape (Csernansky *et al.* 1998; McClure *et al.* 2013; Zierhut *et al.* 2013) and decreased bilateral hippocampal volumes (Nelson *et al.* 1998; Velakoulis *et al.* 1999, 2006; Wright *et al.* 2000; Honea *et al.* 2005; Goldman *et al.* 2008; Walter *et al.* 2012). In our unique population of severely and chronically ill COS patients, we have reported increased ventricular volume and decreased GM volume (Sporn *et al.* 2003; Gogtay *et al.* 2004), as well as decreased hippocampal volume and shape abnormalities (Giedd *et al.* 1999; Gogtay *et al.* 2006; Nugent *et al.* 2007; Mattai *et al.* 2011; Johnson *et al.* 2013). However, the relationship between brain development and clinical outcome has been relatively unexplored.

Lappin *et al.* (2014) examined the relationship between brain volume changes and psychosis in adult first-episode psychosis (FEP) participants ($n = 42$; $n = 20$ with schizophrenia and $n = 22$ with other psychosis) compared with healthy controls ($n = 32$) at baseline and 6-year follow-up. Used as a marker of plasticity and present in 29% of the Lappin study psychosis participants, bilateral hippocampal increase (BHI) was associated with reduced clinical severity and superior clinical, functional and cognitive outcome. No schizophrenia patients showed BHI, but diagnosis did not explain the association between

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BHI and clinical outcome. While less GM volume loss was associated with better employment and global function, GM change was not related to illness course or symptom severity at follow-up (Lappin *et al.* 2014).

In our COS population, we found that rate of GM reduction was related to baseline severity of clinical symptoms [measured by the Scale for the Assessment of Positive Symptoms (SAPS), Scale for the Assessment of Negative Symptoms (SANS) and the Brief Psychiatric Rating Scale for Children], and similar to Lappin *et al.* our group found that GM change was not related to clinical symptoms at follow-up (Sporn *et al.* 2003). During a period of 2–6 years, a higher rate of GM loss was associated with better clinical improvement in COS (Sporn *et al.* 2003) while less GM loss was associated with better global function in adult FEP (Lappin *et al.* 2014). The difference in findings between our group and Lappin's could be explained by progressive change apparent earlier in the course of illness, with a plateau in adolescence (Sporn *et al.* 2003). Other longitudinal studies have similarly observed the inverse relationship between clinical improvement and GM volume loss (Delisi *et al.* 1998; Gur *et al.* 1998).

Mattai *et al.* (2011) looked at the longitudinal development of hippocampal volume during adolescence in our COS probands, their healthy siblings and normal volunteers. There were fixed volume deficits of 6–7% bilaterally, higher than the 4–5% deficit seen in adult schizophrenia, and siblings had no deficits relative to healthy comparisons (Nelson *et al.* 1998; Velakoulis *et al.* 2006; Mattai *et al.* 2011). The results suggest that volume loss is disease-dependent, which is consistent with the current literature (Goldman *et al.* 2008; de Castro-Manglano *et al.* 2011; Mattai *et al.* 2011; Walter *et al.* 2012). Mattai *et al.* (2011) did not examine hippocampal change in relation to clinical status.

We sought to examine hippocampal volume changes in relation to clinical outcome at follow-up, although we could not look at cognitive outcome because of lack of sufficient data. Our hypotheses were: (i) better global function at follow-up will be related to less hippocampal volume decrease; (ii) fewer positive symptoms at follow-up will be related to less hippocampal volume decrease; and (iii) less severe negative symptoms at follow-up will be related to less hippocampal volume decrease.

Method

Subjects

The National Institute of Mental Health (NIMH) COS study has been ongoing since 1990, with national recruitment of patients meeting Diagnostic and Statistical Manual of Mental Disorders (DSM)-IIIR/IV criteria for schizophrenia with the onset of psychosis before the age of 13 years. The COS sample is severely ill, as each patient is typically admitted after trying several antipsychotics with limited results. Diagnosis was determined on the basis of review of medical and academic records, interview with the parents and child, administration of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (Ambrosini *et al.* 1989; Kaufman *et al.* 1997), and in-patient observation with a medication-washout period and drug-free observation in most cases. Exclusionary criteria included medical or neurological illness, substance abuse, or an intelligence quotient (IQ) <70 prior to the onset of psychotic symptoms. Further details are described in previously published material (McKenna *et al.* 1994) (see online Supplementary Appendix S1).

All patients and their full siblings were followed prospectively with anatomical brain magnetic resonance image (MRI) scans and corresponding clinical ratings at 2-year intervals. For this within-subjects study, only COS patients with three or more successive scans between the ages of 10 and 30 years and clinical ratings at the time of last scan between the ages of 10 and 30 years were examined ($n = 27$; 114 scans). All subjects were receiving antipsychotic medication, including clozapine ($n = 17$; with $n = 9$ on more than one study drug), olanzapine ($n = 8$; with $n = 4$ on more than one study drug), quetiapine ($n = 1$) and thiothixene ($n = 1$). Additional medications that complemented primary antipsychotic included risperidone, divalproex, sertraline, haloperidol, clomipramine, lorazepam, clonazepam, phenobarbital and lithium.

Of the 27 participants, follow-up medication was available for all but one. All participants were taking antipsychotic medications over the follow-up period. Of the participants, 20 were prescribed one antipsychotic, and six participants were prescribed two antipsychotics. Of the participants, 17 were prescribed clozapine, four were prescribed olanzapine, and four were prescribed risperidone. Additional antipsychotics included quetiapine (3), ziprasidone (1) and aripriprazole (1) (because some participants were taking more than one antipsychotic, the numbers do not add up to 26).

MRI acquisition and image analysis

T_1-weighted images with contiguous 1.5-mm slices in the axial plane and 2.0-mm slices in the coronal plane were obtained with a three-dimensional spoiled gradient recalled echo in the steady state on a 1.5-T General Electric Signa scanner (USA). Imaging parameters included: echo time of 5 ms, repetition time of 24 ms, flip angle of 45°, acquisition matrix of 256 × 192, number of excitations = 1, and 24 cm field of view. Head placement was standardized (Castellanos *et al.* 1996).

The image files in DICOM (Digital Imaging and Communications in Medicine) format were transferred

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to a Linux workstation for analysis. Subcortical volumes were measured automatically with the FreeSurfer image analysis suite, which is documented and available online (http://surfer.nmr.mgh.harvard.edu/). Individual scans were inspected for significant artifacts or motion disturbances ($n = 1$ proband was excluded from analysis). The automated procedures for subcortical volumetric measurements of different brain structures have been standardized previously (Fischl *et al.* 2001, 2002, 2004; Segonne, 2004, 2007). In our study, total hippocampal volume was calculated as a sum of left and right hippocampal volumes for each study participant. Further details are described in a previously published paper (Mattai *et al.* 2011) (see online Supplementary Appendix S2).

Assessment of clinical outcome

Clinical outcome measures at time of last scan were analysed. Global function was assessed using the Children's Global Assessment Scale (CGAS) score (Shaffer *et al.* 1983). Positive symptom severity was measured using the SAPS (Andreasen & Olsen, 1982; Andreasen, 1984). Negative symptom severity was measured using the SANS (Andreasen & Olsen, 1982; Andreasen, 1983). Over the course of the study, we scored inter-rater reliability with intraclass correlation coefficients (ICCs) for clinical ratings from concomitant raters. ICCs for different groups of child psychiatrists and clinical social workers at five different points of the study ranged from moderate (0.60–0.70) to high (>0.80). Because of the study's time span, there is the possibility for differences among groups of raters; however, we ensured that several raters bridged groups to attenuate possible biases related to study year.

Statistical analysis

Statistical analyses were performed using the R Environment for Statistical Computing (R Development Core Team, 2012). We quantified hippocampal change in three ways: (1) ordinary least squares (OLS) linear regression per person (fit slope of total hippocampal volume for all available scan points); (2) slope of hippocampal volume change given by

$$\frac{\text{Volume}_{\text{LastScan}} - \text{Volume}_{\text{FirstScan}}}{\text{Age}_{\text{LastScan}} - \text{Age}_{\text{FirstScan}}};$$

and (3) percentage change of hippocampal volume change given by

$$\frac{\text{Volume}_{\text{LastScan}} - \text{Volume}_{\text{FirstScan}}}{\text{Volume}_{\text{FirstScan}}}.$$

We explored linear relationships between total hippocampal volume change and clinical outcome using the general linear model.

Both the difference score and OLS estimates of individual change have been shown to be unbiased and intuitive measures of individual change (Willett, 1989). While there are longstanding concerns about the reliability of the difference score, reliability can be adequate when there is not uniform change, and individual change estimates can be precise in spite of poor reliability (Rogosa & Willett, 1983). Non-independence of residuals and serially correlated residuals over time are potential threats to the utility of the estimate for OLS slope per person. However, if the interval between time points is ample (such as a 2-year interval in this study), it is reasonable to assume uncorrelated within-person errors. Also, individual slope estimates remain unbiased in the presence of serially correlated residuals over time (Willett, 1989; Singer & Willett, 2003).

We explored sex, time between scans, baseline hippocampal volume, final hippocampal volume and final total intracranial volume as possible confounds in our analysis. None of these changed the interpretation of the models. Socio-economic status and years ill at last scan were also considered as covariates, but neither accounted for a significant amount of variance in outcome when included in models with brain change measures. Hippocampal trajectories for the left and right hippocampus were similar, so we report results using the total hippocampus (the sum of left and right hippocampal volumes). Data for the left and right hippocampus are reported in online Supplementary Tables S1–S4. OLS-fit slope and difference over time approaches yielded comparable results, so we have reported OLS-fit slope and percentage change results for simplicity.

Results

Demographic measures

Demographic characteristics are reported in Table 1. Briefly, the mean age for all 114 scans was 18.61 years (S.D. = 3.62) and 66.7% of participants were male (Table 1).

Structural brain measures

Change in hippocampal volume as measured by OLS-fit slope and percentage change are shown in Figs 1 and 2. Overall change in volume over time was minimal with a qualitative trend of volume loss (mean OLS-fit slope: −50.95, S.D. = 87.43; mean percentage change: –0.03, S.D. = 0.05) (Figs 1 and 2).

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Table 1. *Demographics for childhood-onset schizophrenia probands*

	Mean (S.D.)
Number of subjects	27
Sex, *n*	
Male	18
Female	9
Total number of scans	114
Mean CGAS	43.59 (14.34)
Mean SAPS	22.75 (17.02)
Mean SANS	40.95 (26.54)
Mean age for all scans, years	18.61 (3.62)
Mean age, years, at	
Scan 1 ($n = 27$)	15.10 (1.82)
Scan 2 ($n = 27$)	17.51 (1.78)
Scan 3 ($n = 27$)	20.24 (2.46)
Scan 4 ($n = 11$)	22.86 (2.96)
Scan 5 ($n = 4$)	22.92 (3.01)
Scan 6 ($n = 2$)	27.15 (1.01)

S.D., Standard deviation; CGAS, Children's Global Assessment Scale; SAPS; Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms.

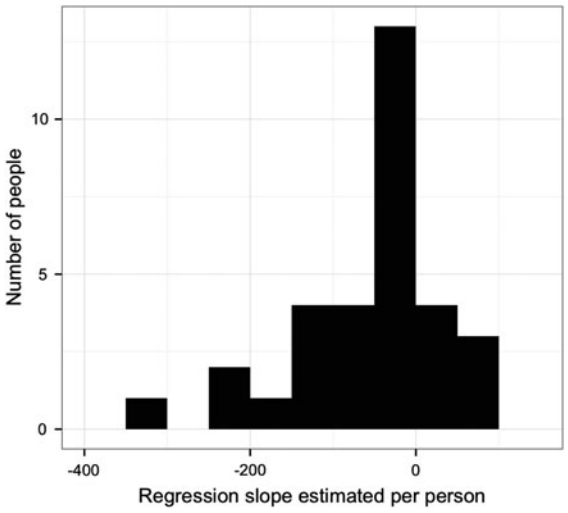

Fig. 1. Change in total hippocampal volume in childhood-onset schizophrenia probands ($n = 27$) from baseline to follow-up as measured by ordinary least squares-fit slope per person (change in volume over change in age). Slope values above 0 indicate an increase of hippocampal volume over time, while slope values below 0 indicate a decrease of hippocampal volume over time.

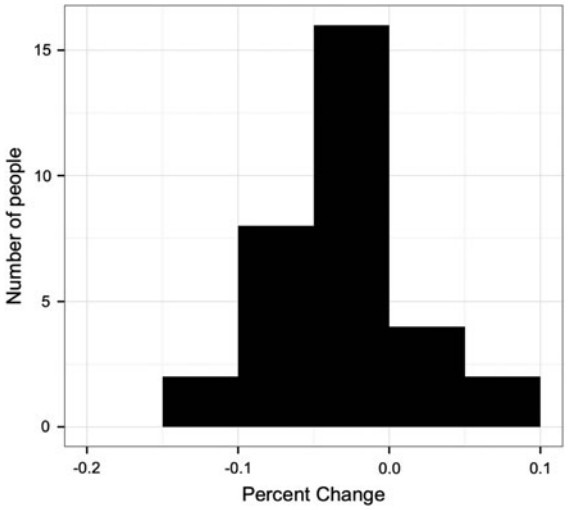

Fig. 2. Change in total hippocampal volumes in childhood-onset schizophrenia probands ($n = 27$) from baseline to follow-up as measured by percentage hippocampal change (change in volume over original volume). Percentage change values above 0 indicate an increase of hippocampal volume over time, while percentage change values below 0 indicate a decrease of hippocampal volume over time.

Relationship between hippocampal change and clinical outcome

Negative symptoms (SANS score) were associated with less hippocampal volume decrease (fit slope: $p = 0.0003$; percentage change: $p = 0.005$), such that less volume decrease was associated with fewer negative symptoms at follow-up (Tables 2 and 3). Positive symptoms (SAPS) were not significantly related to hippocampal change (fit slope: $p = 0.501$; percentage change: $p = 0.695$) (Tables 2 and 3). Higher global functioning (CGAS) was associated with hippocampal change (fit slope: $p = 0.025$; percentage change: $p = 0.043$), with better outcomes associated with less volume loss (Tables 2 and 3). Sex, time between scans, baseline hippocampal volume, final hippocampal volume, and final total intracranial volume had no impact on the interpretation of the models and were not predictors of final clinical outcome.

Discussion

In our population of COS probands, less hippocampal volume decrease was associated with better clinical outcome, specifically better SANS scores indicating less severe negative symptoms and CGAS scores indicating better global functioning. We hypothesize a possible plastic or compensatory role of the hippocampal pathway in these cases. We present a partial replication of Lappin *et al.* (2014) with respect to hippocampal volume change and clinical outcome in schizophrenia. Our study differed from Lappin's in important facets, particularly highlighted in our population of young, chronically ill schizophrenia patients as opposed to FEP adult patients, the majority of whom suffered from acute illness.

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Table 2. *Predictors of final global function and symptom severity: hippocampal volume change (in this case, OLS-fit slope per person) and clinical ratings at baseline*[a]

	Ratings measure	Predictor of final clinical outcome	Estimate (standard error)	*t*	*p*
No covariates	SANS	Fit slope per person	−0.1688 (0.0399)	−4.225	0.0003*
	SAPS	Fit slope per person	−0.0206 (0.0301)	−0.684	0.5008
	CGAS	Fit slope per person	0.0689 (0.0290)	2.377	0.0254*
Baseline rating as covariate	SANS	Fit slope per person	−0.1451 (0.0380)	−3.815	0.0008*
		SANS at baseline	0.2595 (0.1094)	2.371	0.0261*
	SAPS	Fit slope per person	−0.0203 (0.0302)	−0.672	0.5080
		SAPS at baseline	0.1305 (0.1422)	0.918	0.3682
	CGAS	Fit slope per person	0.0650 (0.0272)	2.386	0.0253*
		CGAS at baseline	0.3682 (0.1757)	2.096	0.0468*

OLS, Ordinary least squares; SANS, Scale for the Assessment of Negative Symptoms; SAPS; Scale for the Assessment of Positive Symptoms; CGAS, Children's Global Assessment Scale.

[a] Results are shown for unadjusted slope values, fit slope adjusted for baseline ratings, and baseline clinical ratings adjusted for fit slope.

* Significant ($p < 0.05$).

Table 3. *Predictors of final global function and symptom severity: hippocampal volume change (in this case, percentage change) and clinical ratings at baseline*[a]

	Ratings measure	Predictor of final clinical outcome	Estimate (standard error)	*t*	*p*
No covariates	SANS	Percentage change	−253.0320 (81.4890)	−3.105	0.0047*
	SAPS	Percentage change	−22.5380 (56.8150)	−0.397	0.6951
	CGAS	Percentage change	115.2960 (54.1240)	2.130	0.0432*
Baseline rating as covariate	SANS	Percentage change	−211.2839 (76.1156)	−2.776	0.0105*
		SANS at baseline	0.2957 (0.1194)	2.476	0.0207*
	SAPS	Percentage change	−21.7216 (57.0217)	−0.381	0.7067
		SAPS at baseline	0.1306 (0.1432)	0.912	0.3711
	CGAS	Percentage change	106.6535 (51.2106)	2.083	0.0481*
		CGAS at baseline	0.3655 (0.1801)	2.030	0.0536

SANS, Scale for the Assessment of Negative Symptoms; SAPS; Scale for the Assessment of Positive Symptoms; CGAS, Children's Global Assessment Scale.

[a] Results are shown for unadjusted values of percentage change, percentage change adjusted for baseline ratings, and baseline clinical ratings adjusted for percentage volume change.

* Significant ($p < 0.05$).

Hippocampal volume reduction occurs during normal adolescence (Giedd *et al.* 1999; Gogtay *et al.* 2006). In the case of COS, we suggest a relationship between hippocampal volume reduction and negative symptoms as well as global functioning. To supplement our study, we cross-sectionally analysed hippocampal volume and clinical outcome at baseline and final time points. Neither baseline nor final global function and clinical severity were associated with baseline or final hippocampal volume. We also found no relationship between hippocampal volume change and baseline clinical outcome. We suggest that the longitudinal trajectory of the hippocampus relates to final clinical outcome and specifically to negative symptoms.

The hippocampus is a highly plastic region that can be indicative of disease state. In our pediatric cohort, we have a wide variety of clinical outcomes (Sporn *et al.* 2007). For hippocampal shape in COS, positive symptom severity has been associated with inward deformations in the anterior hippocampus, and better overall functioning has been associated with outward hippocampal deformation (Johnson *et al.* 2013). Bilateral hippocampal reductions in psychotic adults

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are associated with poor clinical outcome (de Castro-Manglano *et al.* 2011), greater duration of illness (Velakoulis *et al.* 1999; Chakos *et al.* 2005; Brambilla *et al.* 2013), lower health status, lower levels of education, and higher levels of positive and negative symptoms (Brambilla *et al.* 2013). Mechanisms of hippocampal change are unclear, whether they are environmental, due to medication or related to disease (Nelson *et al.* 1998).

Our results add to the body of literature suggesting that clinical severity and outcome can reflect poor hippocampal plasticity in schizophrenia, so hippocampal pathways can be considered for potential treatment interventions. Theories to consider include the cortisol and dopamine hypotheses. The cortisol hypothesis proposes that stress is associated with reduced hippocampal neurogenesis, changes in hippocampal neuronal function, and decreased hippocampal volume (Mondelli *et al.* 2010; Grace, 2012; Collip *et al.* 2013). The dopamine hypothesis suggests that current D2 antagonist interventions target the connective pathway further downstream the connective pathway from the hippocampus at the nucleus accumbens, mostly addressing positive symptoms (Lodge & Grace, 2011; Grace, 2012). Future work can focus on therapeutic developments that selectively target the hippocampus further upstream the dopamine pathway. Such interventions might help restore appropriate hippocampal regulation in the disease state.

We acknowledge the limitations of our study. Looking only at global function, negative symptoms and positive symptoms in relation to hippocampal volume change, we replicated a small proportion of the Lappin group's study (Lappin *et al.* 2014) in our sample. We found our subtle volume changes to be almost negligible with very flat slopes in the trajectory of hippocampal volumes. We would prefer to have had a larger sample size that met criteria for analysis because we cannot account for the immense heterogeneity of disease progression in schizophrenia. We speculate that initiation of clozapine for this mostly treatment-refractory patient group may have resulted in a greater improvement in negative symptoms across time and thus stronger relationship for this measure. A further limitation is the unknown specificity of this finding. It has been suggested in cross-sectional studies that larger hippocampal volume represents a plastic compensatory response in attention-deficit/hyperactivity disorder (Plessen *et al.* 2006).

In addition, we cannot accurately determine drug effects, as all patients were receiving medication. The literature is contradictory, with studies indicating that antipsychotic medications can help maintain hippocampal volumes (Lieberman *et al.* 2001; Chakos *et al.* 2005; Walter *et al.* 2012), exacerbate deflation of hippocampal volume (Brambilla *et al.* 2013; Zipursky *et al.* 2013), or that drug effects do not explain volume differences (Velakoulis *et al.* 1999; Mattai *et al.* 2011; Lappin *et al.* 2014). Some studies also suggested that type of antipsychotic medication could determine effects on hippocampal volumes (Lieberman *et al.* 2001; Zipursky *et al.* 2013), while other studies have not found significant volume differences between types of antipsychotics (Velakoulis *et al.* 2006; McClure *et al.* 2013). Our study is unique in that a large percentage (70%) of our group was maintained on clozapine, for which there is no long-term hippocampal data available in the literature.

Ongoing studies are examining hippocampal development in COS probands using 7-T MRI to isolate subnuclei within the hippocampus that may change in relation to clinical outcome.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291715000677

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Declaration of Interest

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