QUALITY OF LIFE IN PSYCHOTIC ILLNESS:

BASELINE AND PROSPECTIVE DETERMINANTS IN FIRST EPISODE AND CHRONIC PSYCHOSIS COHORTS

A thesis submitted to the National University of Ireland, Galway for the fulfilment of the requirements of the degree of Doctor in Medicine (MD)

by

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Table of Contents

Chapter 7

Chapter 8

List of Figures

List of Tables

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Declaration

I, the Candidate, certify that the Thesis is all my own work and that I have not obtained a degree in this University or elsewhere on the basis of any of this work.

Signed:

Declaration of contribution:

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FEP study:

Dr McInerney conducted the clinical assessments and completed the statistical analysis at the follow up period.

Chronic study:

Dr McInerney devised the study, undertook the patient assessments at all stages of the 10 year study and enlisted the assistance of nursing staff to complete the functional outcome measures. He also conducted the statistical analysis and wrote the manuscript.

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To my father Niall, miss you every day.

Abbreviations

AC-PC	Anterior Commissure-Posterior Commissure
ADLs	Activities of Daily Living
APn	antipsychotic naïve
Avg	Average
b	Standardised regression co-efficient
BELS	Basic Everyday Living skills
BHI	Bilateral Hippocampal Volume
BPAD	Bipolar Affective Disorder
CB	Cannabinoid
CI	Confidence Interval
CPQ	Community Placement Questionnaire
CSZ	Chronic Schizophrenia
DALYs	Disability-Adjusted Life Years
DICOM	Digital Imaging & Communication in Medicine
DSM	Diagnostic Statistical Manual

DTI	Diffusion Tensor Imaging
DUP	Duration of Untreated Psychosis
FE	First episode
FEP	First Episode Psychosis
FEM	First Episode Psychotic Mania
FES	First Episode Schizophrenia
FLAIR	Fluid Attenuated Inversion Recovery
GAF	Global Assessment of Function
GBD	Global Burden of Diseases
GMV	Grey Matter Volume
HC	Healthy Control
HDRS	Hamilton Depression Rating Scale
HSE	Health Services Executive
ICV	intracranial fluid
ICT	Intensive Community Treatment
LTFU	Lost To Follow Up

LV	Lateral Ventricle
MADRS	Montgomery Asberg Depression Rating Scale
MD	Doctor of Medicine
MANSA	Manchester Short Assessment of Quality of Life,
MPRAGE	Magnetisation Prepared Rapid Gradient Echo
MRI	Magnetic Resonance Imaging
n	Number
NC	Normal Controls
NIFTI	Neuroimaging Informatics Technology Initiative
NOS	Not Otherwise Specified
QDEC	Query Design Estimate Contrast
oQoL	Objective Quality of Life
QoL	Quality of Life
p	Probability
PANSS	Positive and Negative Syndrome Scale
PNOS	Psychosis Not Otherwise Specified

PSYCH-BASE	Psychiatric Symptoms You Currently Have—Baseline Version
PSYCH-UP	Psychiatric Symptoms You Currently Have- Follow Up
QLS	Quality of Life Scale
r	Correlation
SBS	Social Behaviour Schedule
SCID	Structural Clinical Interview for DSM IV
SCID-NP	Structural Clinical Interview for DSM IV – Non Patient Edition
SCZ	Schizophrenia
SD	Standard Deviation
SF	Social Functioning Score
SMcI	Shane McInerney
sMRI	Structural Magnetic Resonance Imaging
SPM	Statistical Parametric Mapping
SPSS	Statistical Package for Social Sciences
sQoL	Subjective Quality of Life
SSD	Schizophrenia Spectrum Disorder

STG	Superior Temporal Gyrus
TAPS	Team for the Assessment of Psychiatric Services
TAU	Treatment as Usual
TBV	Total Brain Volume
TE	Echo Time
TI	Inversion Time
WBV	Whole Brain Volume
WHO	World Health Organisation
WQLI	Wisconsin Quality of Life Index
WMV	White Matter Volume
YMRS	Young Mania Rating Scale

Abstract

The overall aim of this thesis was to longitudinally assess determinants of quality of life in first episode and chronic psychosis patient cohorts.

The Galway First Episode Psychosis Cohort

Background:

In this study, first episode psychosis (FEP) patients were followed up after a minimum of three years in order to determine the extent to which clinical and morphometric indices were associated with quality of life (QoL).

Method:

45 patients were recruited into the study and a proportion of these (n=32) underwent clinical and neuroimaging investigations at both baseline and follow up.

Results:

Lower QoL was predicted clinically by higher baseline negative symptoms and improvement in negative symptoms predicted higher QoL 3 years later. From a neuroimaging perspective, left lateral ventricular volume enlargement over the follow up period was associated with lower QoL.

Conclusions:

This study demonstrated that it was the trajectory of clinical and morphometric measures over time, particularly with respect to negative symptoms and left lateral ventricular volume, that are most associated with QoL as an outcome measure. Such measures may represent markers of a neuroprogressive process that ultimately determines the functional outcome after the onset of psychotic illness.

QoL of long-stay psychiatric patients transferred into the community

Background: This study comprised a cohort of former long-stay institutionalised patients who were subsequently transferred into local community settings.

Method: 87 former long-stay psychiatric patients, the majority of whom had a diagnosis of schizophrenia, were assessed at baseline (one month prior to hospital closure) and 10 years later on a range of QoL and functional measures. The QoL measure (Quality of Life Scale) was only conducted at the follow up period.

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Results: Improvements were noted for both QoL and social functioning at 10 year follow up. Linear regression analysis found that baseline social behaviour predicted QoL at follow up.

Conclusion: This study demonstrates that transfer into the community from a psychiatric institution is associated with long-term improvement in QoL and social functioning, even in individuals who have spent large periods of time in such environments. Those patients who demonstrated the greatest improvement in QoL had higher baseline social skills.

Chapter 1

Introduction

Quality of Life in First Episode Psychosis

1.1 Psychosis

Psychosis is a feature of several major mental illnesses such as schizophrenia and bipolar disorder and is typically characterized by a distorted sense of objective reality. The key symptoms that define psychotic disorders are hallucinations, delusions, disorganized speech, catatonia and negative symptoms (American Psychiatric Association, 2013). Psychotic disorders are frequently classified as either affective or non-affective psychoses, dependant on the role that affective symptoms play in presentation of the illness (Table 1.1). As well as affect, an assessment of the duration of psychosis, history of substance abuse and the impact of the condition on the individual's level of functioning is helpful in distinguishing between the various psychotic illnesses (Owen et al., 2016).

Table 1.1 Non-affective and Affective Psychoses

Non-affective psychotic disorders:	**Affective psychotic disorders:**
Schizophrenia	Bipolar disorder with psychotic features
Schizoaffective disorder	Major depressive disorder with psychotic features
Substance-induced psychotic disorder	
Delusional disorder	
Psychotic disorder due to a GMC*	
Brief psychotic disorder	
Psychotic disorder not otherwise specified	
Substance-induced psychotic disorder	

*General Medical Condition

The DSM-5 criteria for psychotic disorders are based on the categorical approach advocated initially by Emil Kraepelin (1855-1926) and include a large number of categories (of psychosis). Kraepelin believed that detailed empirical observation of mental illness over time lead to differentiation of one form of illness over another, which in time could lead to finding specific

aetiologies. Thus Kraepelin distinguished between dementia praecox/schizophrenia and manic depression, while others such as Eugen Bleuler (1857-1959) argued for a spectrum illness model such as a 'general psychosis syndrome' due to the heterogeneity of psychotic disorders (Reininghaus et al., 2013). One argument for the classification of psychotic disorders on the basis of affect (as in this thesis), is that the presence of mood symptoms in psychosis has been found to have a more positive prognostic outcome compared to the non-affective psychotic disorders where negative symptoms are more pronounced and prognosis is poorer (Peralta and Cuesta, 2009).

1.1.1 History, diagnosis and symptoms of psychosis

Psychotic illnesses are amongst the most disabling of all psychiatric conditions. They often manifest in late adolescence or early adulthood and frequently have a significant deleterious effect on the individual's quality of life and functioning. While some people have a single psychotic episode which resolves with treatment, others suffer a prolonged and often lifelong illness despite multiple pharmacological and psychological interventions.

Diagnostic uncertainty is often present during a First Episode of Psychosis (FEP) due to the frequent fluctuating nature of affective and psychotic symptoms that are evident during an episode (Bromet et al., 2005; Kim et al., 2011). To date, diagnostic stability at a FEP has been demonstrated to be superior for schizophrenia and bipolar disorders compared to schizoaffective disorder which has been noted to display a diagnostic shift more frequently when compared to other disorders such as bipolar disorder or schizophrenia (Schwartz et al., 2000; Amini et al., 2005; Salvatore et al., 2009). Risk factors consistently identified for a diagnostic shift to schizophrenia relate to poorer premorbid functioning and longer duration of untreated psychosis (DUP) (Whitty et al., 2005; Salvatore et al., 2009).

In addition to a difference in prognosis between affective and non-affective psychotic disorders, differing medical and psychosocial treatments are often indicated (Bola et al., 2009). Thus it can be argued that diagnostic re-evaluation throughout the course of illness for all psychotic disorders is necessary and clinically meaningful (Schwartz et al., 2000).

1.1.2 Aetiology of psychosis

Family, twin and adoption studies indicate an important genetic component to the development of psychosis. The lifetime risk of schizophrenia is increased from 1% in the general population to approximately 6-15% in those who have a first-degree relative with schizophrenia and to approximately 48% when both parents have a diagnosis of schizophrenia (Kirkpatrick et al., 2000). Similarly in bipolar disorder, the lifetime prevalence of approximately 1% in the general population is increased to between 5-10% where a first-degree relative has bipolar disorder (Craddock and Sklar, 2013). With respect to environmental factors; peri-natal complications (Crow et al., 1991), immigration (Boonstra et al., 2011) , cannabis abuse (Casadio et al., 2011) , ethnicity (Fearon et al., 2006) and significant adverse life events such as childhood trauma (van Os et al., 1994; Kelleher et al., 2013) are all factors demonstrated in a number of longitudinal studies to be associated with at least a two-fold increase in the risk of subsequently developing schizophrenia (Arseneault et al., 2002; Zammit et al., 2002).

1.1.3 Burden of psychosis

Psychotic illnesses have a significant impact on the patient, their care-givers and have a financial impact on society. The percentage of disability-adjusted life years (DALYs) was 7.4% for schizophrenia and 7.0% for bipolar disorder, relative to all mental and substance use disorders

(Whiteford et al., 2013). Psychotic relapse occurs in approximately 50% of FEP patients within 3 years. Several factors have been associated with psychotic relapse including treatment non-adherence (Üçok et al., 2011), limited insight into one's illness (Lauber and Rössler, 2007), comorbid depression, comorbid psychoactive substance misuse (Moeller et al., 2006) and adverse life events (Kazadi et al., 2008).

1.2 Psychosis and impact on Quality of Life

Having discussed the diverse nature of psychotic illnesses above, the effect that these illnesses have on the Quality of Life (QoL) of those affected will now be discussed.

1.2.1 Quality of Life definition and assessment

Psychotic disorders such as schizophrenia and bipolar disorder carry a considerable risk for impaired functioning and poor QoL (Norman et al., 2000; Renwick et al., 2015) The World Health Organization (WHO) defines QoL as an 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 (The WHOQOL Group, 1998). This definition reflects a subjective evaluation of the effects of illness and health interventions on QoL. Given the significant impact that a psychotic illness can have on an individual's functioning, evaluating QoL is increasingly viewed as an important clinical assessment. Patient-reported outcomes (PROs) are increasingly being attained in caring for patients with psychosis. The assessment of QoL is one such outcome measure; with treatment satisfaction and the therapeutic relationship within their circle of care other measureable PROs (Reininghaus and Priebe, 2012).

A primary author in this area, Anthony Lehman described how QoL encompassed functional status, access to opportunities and a sense of well-being (Lehman, 1996). He maintained that QoL had both subjective and objective domains and that QoL offered a unique perspective on the value of health care delivered to those with psychotic illness. While QoL has been recognised as an important outcome measure for schizophrenia, the particular determinants of QoL for individuals with schizophrenia remain uncertain (Eack and Newhill, 2007).

QoL is frequently considered to comprise a subjective component (sQoL) measuring life satisfaction, and a more objective component (oQoL) integrating socio-economic indicators such as the availability of access to finances, housing and a social network (Gardsjord et al., 2016a). In fact, most QoL measures are a mixture of both objective and the subjective questions and this allows for a comprehensive QoL life assessment within the one instrument (Nishiyama and Ozaki, 2010). While both subjective and objective QoL assessments were assessed in this thesis, the primary focus will be on the objective assessment used, the Quality of Life Scale (QLS) (Heinrichs et al., 1984). The QLS is one of the most widely used QoL scales in schizophrenia and FEP studies. While it was originally designed to assess deficit syndrome symptoms in schizophrenia, prominent researchers in the field of QoL research have recognised the QLS as a comprehensive broad spectrum measure of multiple outcome domains in psychosis (McGorry et al., 1996). The QLS assesses the richness of the patient's personal experience, the quality of their interpersonal relations and their productivity in occupational roles and as such is able to encompass the depth of life experience in both FEP and chronic psychosis cohorts.

A number of clinical factors have been associated with diminished QoL, including depressive symptoms, negative symptoms, poor premorbid functioning and longer DUP (Sim et al., 2004; Melle et al., 2005; Cotton et al., 2010; Renwick et al., 2015). These findings have proved difficult to replicate, partially due to the varying definitions and methodologies utilised with respect to QoL based research. In recent years, there is a greater recognition that QoL is a

multidimensional construct incorporating assessments of multiple life domains and can act as an important link between a physician's assessment of need for treatment of illness and patient's perspective on life as a whole. Without detracting from the importance of including patient's views, objective assessments of functional outcome can help determine both the type and impact of therapeutic strategies to enable improved functional status and subjective well-being (Renwick et al., 2015).

1.2.2 Clinical correlates of QoL in psychosis

A greater awareness of the clinical and socio-demographic factors that can predict QoL would allow appropriate interventions to reduce illness burden and increase future QoL. Assessment of psychopathology is important for diagnosis and management. However, although psychopathology at baseline may predict future QoL, increasing evidence suggests that other factors such as occupational and social functioning are at least as predictive of future QoL (Malla and Payne, 2005; Renwick et al., 2015).

Table 1.2 includes the main studies exploring QoL in FEP samples. These studies involve differing FEP cohorts; those with exclusively FE mania cohorts (Michalak et al., 2013; Oldis et al., 2016), those with both affective and non-affective FEP cohorts (Melle et al., 2010; Renwick et al., 2015), with one study focusing predominantly on a FE schizophrenia population (Whitty et al., 2004). Improvement in QoL over time on both sQoL and oQoL assessments were noted, with an improvement in symptomatology (both positive and negative symptoms) frequently correlated with improved sQoL (Melle et al., 2010; Thorup et al., 2010). Melle and colleagues (2010) demonstrated that higher sQoL was statistically significantly associated with having more years of education and with being employed at follow up. In the same paper, neither DUP nor other demographic characteristics were significantly associated with change in sQoL (Melle et al., 2010). Perhaps surprisingly, Priebe and colleagues found that patients with schizophrenia

reported more favourable sQoL scores than those with mood or anxiety disorders (Priebe et al., 2010). A potential explanation for this finding is that some patients with schizophrenia may adapt to the experience of living with their disorder and have lower expectations of their life leading to higher satisfaction ratings (Lehman, 1996; Atkinson et al., 1997). They may also lack insight into the severity of their illness, leading to a higher than expected QoL being reported.

While sQoL and oQoL are independent assessments, Whitty and colleagues found a significant correlation between the objective QLS measure and the subjective WHOQOL-Bref measure, indicating a marked similarity between patients and clinicians ratings of QoL in their sample (Whitty et al., 2004). However, subjective and objective ratings of QoL in a chronic psychosis cohort have previously demonstrated a low correlation, with clinicians and patients identifying different factors as predictive of QoL (Narvaez et al., 2008). This potentially indicates that FEP and stable schizophrenia patients differentially interpret their QoL experience and that sQoL and oQoL, at least in those with more chronic illness, may represent a different expression of experience. Priebe and colleagues found that patients admitted during their FES (first episode of schizophrenia) had lower sQoL compared with both chronic patients and healthy cohorts (Priebe et al., 2010). A meta-analysis found that psychotic symptoms had a small but significant relationship with QoL in schizophrenia and that more focus should be on psychosocial treatments in order to have an impact on QoL beyond that achieved when clinical symptoms improve (Eack and Newhill, 2007). However, despite reduced symptomatology associated with improved sQoL and oQoL (Eack and Newhill, 2007; Thorup et al., 2010), a beneficial impact of psychosocial interventions on QoL has not yet been consistently demonstrated (Thorup et al., 2010). Gardsjord found that a decrease in depressive symptoms was associated with improvement in sQoL over a 10 year follow up period but similarly did negative symptoms but to a lesser extent (Gardsjord et al., 2016b). This suggests that treatment should be focussed on general psychopathology (such as depressive symptoms) and functioning to improve QoL.

Table 1.2 FEP Quality of Life studies

Study	QOL Measure	Methodology	Main Findings
Oldis et al (2016)	QLS	FE Mania (n=60), followed for 18 months	QLS improved over time. Significant correlation between YMRS and MADRS at QLS at 18 months.
Gardsjord et al (2016a)	Lehman's QOLI	FEP (n=272) at baseline. 186 followed up 10 years later.	sQoL improved significantly over time. Increased daily activities and a decrease in depressive symptoms were associated with a positive sQoL at follow up.
Renwick et al (2015)	Wisconsin QQLI For clients and Providers	FEP (n=222) affective and non-affective types. 128 completed sQoL; 178 clinician oQoL	Impairment in psychological wellbeing noted but ADL measurements were normal. sQoL and oQoL correlated with ratings for occupation, social relations and ADLs but not wellbeing or symptomatology.
Michalak et al (2013)	Q-LES-Q	FE Mania (n=63) aged 16-34 followed up for 18 months	QLS improved over time. Length of illness and depressive symptoms predicted QoL at follow up.
Melle et al (2010)	Lehman's QOLI	Consecutive FEP (n=112) over 2 years.	Improvement in sQoL in FEP after 2 years of treatment. Few changes in oQoL.
Thorup et al (2010)	Lancashire QoL Profile	OPUS Trial. FEP (N=280) followed up for 2 years. ICT compared to TAU.	The intensive treatment did not differ in QoL from TAU. QoL correlated with both positive and negative symptoms.
Whitty et al (2004)	WHO-BREF QLS	FEP =72 followed up after 4 years. 76% had schizophrenia.	Patients had moderate impairment in their sQoL and oQoL at follow up. No baseline measures obtained. Strong correlation between sQoL and oQoL.
Priebe et al (2000)	Lancashire QoL Profile or MANSA	Pooled analysis of 16 studies. N=3,936. 71% had schizophrenia	Symptomatology more strongly associated with sQoL in neurotic than in mood and schizophrenia.
Ho et al (1998)	PSYCH-BASE PSYCH-UP	FES (n=50), 2 yrs follow up	Baseline negative symptoms (<13) were associated with poor QoL at follow up.

ADLs = Activity of Daily Living; FE = First Episode; FEP = First Episode Psychosis; ICT = Intensive Community Treatment; MADRS = Montgomery Asberg Depression Rating Scale; MANSA= Manchester Short Assessment of Quality of Life, Psychiatric Symptoms You Currently Have—Baseline Version (PSYCH-BASE), Follow Up (PSYCH-UP); oQoL = objective Quality of Life; QLS = Quality of Life Scale; sQoL = subjective Quality of Life, TAU = Treatment as Usual; YMRS = Young Mania Rating Scale; WQLI=Wisconsin Quality of Life Index.

1.3 Benefit of longitudinal studies in first episode psychosis (FEP)

Longitudinal research is best placed (compared to other research designs such as cross-sectional studies) to characterize the clinical course of an illness due to the chronological course of investigation over a defined period of time. One such FEP longitudinal study of 10 year duration, found sustained periods of symptom remission following first presentation for psychosis (46% were symptom free for at least 2 years). Those with an affective disorder in this study had a higher rate of recovery than the non-affective type of psychosis (Morgan et al., 2014a). The purpose of the present study is to assess how a variety of psychosocial measures in a FEP cohort are related to QoL measured 3 years later. As discussed later in the thesis, a longitudinal research design can also be used to assess if the development and/or change in structural brain abnormalities over time are related to variation in QoL.

1.4 First Episode Psychosis (FEP)

The first psychotic episode is a crucial period for intervention as FEP can have a deleterious and devastating effect on individuals' future QoL and functioning. Loss of contact with family and friends, loss of employment and deterioration in functioning are all possible consequences of developing a psychotic illness (Thorup et al., 2010). Early intervention may improve symptomatology, functioning and QoL (Van Der Gaag et al., 2013; Morgan et al., 2014b). Examination of FEP patients using a longitudinal design, as in this thesis, allows for precise investigation into clinical and functional outcomes which can potentially inform future interventions. Additionally, one can examine if there are differential clinical and functional outcomes in affective compared to non-affective psychosis cohorts.

1.4.1 First Episode Manic Episode and QoL

There is a paucity of research to date examining QoL longitudinally in individuals presenting with a first episode of psychotic mania (FEM), with only two recent studies (see Table 1.2) of note examining this construct (Michalak et al., 2013; Oldis et al., 2016). The first one noted that while baseline QoL was mildly impaired, there was a general trend towards improvement over time, with duration of illness and baseline depressive symptoms predictive of QoL at six-month follow-up (Michalak et al., 2013). The second, an 18-month longitudinal study, which assessed patients on the QLS scale, found pre-morbid adjustment and depressive symptoms during the follow-up period as significantly associated with subsequent QoL (Oldis et al., 2016).

1.4.2 Duration of Untreated Psychosis in relation to QoL

Duration of Untreated Psychosis (DUP) is the period of time from the emergence of psychotic symptoms to treatment with antipsychotic medication (de Haan et al., 2003). DUP has been shown to be associated with symptom severity, but its relationship to QoL is unclear. Although some investigators have demonstrated that a longer DUP is correlated with more pronounced negative symptoms at follow up (Edwards et al., 2002; Harrigan et al., 2003; Malla et al., 2004), this is not a consistent finding (Addington et al., 2004; Harris et al., 2005; Jeppesen et al., 2008; Melle et al., 2008). Similarly, there is inconsistent and limited evidence to date of a relationship between DUP and subsequent functional outcome (Marshall et al., 2005; Perkins et al., 2005). However, meta-analytic data has demonstrated statistically significant associations between DUP and several clinical outcome measures over the first year of treatment, with a longer DUP associated with higher positive and negative symptoms and poorer social functioning (Marshall et al., 2005; Perkins et al., 2005; Chang et al., 2012; Hill et al., 2012; Tang et al., 2014). Longer longitudinal studies (>10 years) have demonstrated that a longer DUP (categorised into short,

medium and long duration groups) predicted poorer remission status, more severe positive and negative symptoms (Hill et al., 2012; Tang et al., 2014), with an adverse impact on social functioning also noted (Hill et al., 2012). The relationship between DUP and QoL is unlikely to be linear but rather multifactorial and related to clinical symptoms and social functioning.

1.4.3 Structural neuroanatomical findings in FEP at baseline assessment

FEP is a heterogeneous group of illnesses and includes (as discussed in section 1.1.1) several different mental health disorders including categories such as substance induced psychotic disorders and psychotic disorder not otherwise specified (PNOS). Multiple structural MRI studies have been conducted to date in FEP. Enlargement of lateral ventricles (LVs) (Vita et al., 2006, 2012; Fusar-Poli et al., 2013), reduced hippocampal volume (Wright et al., 2000; Vita et al., 2006) and reduced global cerebral volume have been most frequently demonstrated (Wright et al., 2000; Vita et al., 2006, 2012; Fusar-Poli et al., 2013) although results have been somewhat inconsistent (Table 1.3). Both FE schizophrenia and bipolar samples appear to exhibit cortical and subcortical structural deficits in FEP (Olabi et al., 2011; Watson et al., 2012) with an adolescent FEP study noting no significant differences in brain structure between affective and non-affective psychosis groups when compared (de Castro-Manglano et al., 2011).

Table 1.3 Meta-Analyses / Systematic Reviews of structural MRI studies in psychosis*

Study	Sample	N (Avg)	Region Affected	Effect Size (d)
Wright et al., (2000) (Medicated)	CS/FES/SSD	27	↑Left LV ↓ WBV ↓Left Hippocampus ↑Right Hippocampus	0.51 -0.25 -0.42 -0.38
Vita et al., (2006) (Medicated)	FES	31	↑Left LV ↓Left Hippocampus ↑Right Hippocampus ↓ WBV	0.61 0.59 0.66 0.24
Arnone et al.,(2008) (Medicated)	FES	34	↓ Corpus Callosum area	0.70
Adriano et al., (2012) (Medicated)	FES	30	↓ Right Hippocampus	-0.56
DePeri et al., (2012) (Medicated)	FES	35	↑Left LVs ↓ GM	L=0.49, R=0.40 0.38
Haijma et al., (2013) (AP Naïve)	CS/FES/SSD	25	↓Caudate nucleus ↓Left Hippocampus ↓ GM	0.38 -0.43 -0.36
Fusar-Poli et al., (2013) (Medicated)	CS/FES/SSD	41	↑LVs ↓ WM	0.45 -0.25
Haijma et al., (2013) (Medicated)	CS/FES/SSD	28	↑ LVs ↓ GM ↑ Third Ventricle	0.43 -0.43 0.51

*Adapted from (Hager and Keshavan, 2015). Abbreviations: Avg = Average; AP =antipsychotic naive; CS = chronic schizophrenia; FES =first-episode schizophrenia; GM =Grey Matter; L=left; LV =Lateral Ventricle; R =right; SSD =schizophrenia spectrum disorders; WBV =Whole Brain Volume; WMV =White Matter Volume.

1.4.4 Longitudinal brain imaging studies in FEP

Longitudinal neuroimaging studies of FEP may provide information on the progression of anatomical changes in the brain and their association with the clinical course of psychotic illness. Indeed, FEP has been associated with a number of longitudinal brain changes with the most consistent of these relating to progressive LV enlargement (Steen et al., 2006; Cahn et al., 2009; Kempton et al., 2010a), and a progressive reduction in total GM volume (Steen et al., 2006; Zipparo et al., 2008; Gutierrez-Galve et al., 2015), but findings have been somewhat inconsistent (Schaufelberger et al., 2011; Haukvik et al., 2016). It is unclear at present if progressive brain structural deficits are associated with QoL as this outcome has to date (to our knowledge) not been investigated in brain imaging studies.

1.4.5 Clinical correlates with neuroimaging findings

Brain changes emerging longitudinally after FEP are reported (Steen et al., 2006; Cahn et al., 2009), however the extent of the clinical and socio-demographic factors associated with such brain changes have yet to be fully elucidated. Several demographic and clinical factors have been reported to affect regional brain volumes longitudinally subsequent to a FEP. These potential factors include; DUP, symptom severity, antipsychotic treatment and cannabis use (Zipursky et al., 2013). DUP, as described, has been found to negatively impact clinical outcomes and QoL in FEP. Brain regional deficits in the temporal lobe, caudate nucleus and hippocampus have been found to be inversely correlated with DUP (Matsumoto et al., 2001; Lappin et al., 2006; Crespo-Facorro et al., 2007; Guo et al., 2013), however several studies have not confirmed these findings (Hoff et al., 2000; Ho et al., 2003, 2005; Ebdrup, 2010) suggesting any such association at least requires further replication.

Symptom severity has also been associated with several regional brain volume alterations over time in individuals with FEP (Lieberman et al., 2005; van Haren et al., 2008; Ho et al., 2011; Arango et al., 2012). Progressive LV enlargement for example has been associated with greater overall psychopathology (Rais et al., 2008; Cahn et al., 2009). Negative symptoms have been shown to be inversely correlated with frontal, temporal, parietal lobe, hippocampal and total GM volumes (Matsumoto et al., 2001; Hazlett et al., 2008; Reig et al., 2010, 2011; Bergé et al., 2011; Arango et al., 2012). Positive symptoms have been shown to be inversely correlated with frontal lobe volumes (Thompson et al., 2001), and correlated with LV volume (Cahn et al., 2009). Lappin et al (2013) found that bilateral hippocampal volume was associated with good clinical, cognitive and functional outcome while Roiz-Santianez and colleagues found that greater volume reduction of the caudate was associated with greater clinical improvement (Lappin et al., 2013; Roiz-Santiáñez et al., 2014). No significant progressive changes in GM regional volumes were observed in either the FESZ or FEAP group overall. However, FES subjects with a non-remitting course showed GM decrements in the left superior temporal gyrus (STG) and insula relative to remitted FES subjects (Rosa et al., 2014).

Antipsychotic medications have also been associated with greater grey matter deficits (Cahn et al., 2002a; Ho et al., 2011). A differential effect of typical and atypical antipsychotic agents has been demonstrated, including increased basal ganglia volume noted with typical but not atypical antipsychotic agents (Scherk and Falkai, 2006; Ebdrup et al., 2013). In addition, a differential effect of antipsychotic agents regarding hippocampal (Chakos et al., 2005), frontal lobe (van Haren et al., 2007) and total GM (Smieskova et al., 2009; Vita et al., 2015) volume have been reported, however these findings have not consistently been demonstrated (Crespo-Faccoro et al., 2008). Indeed, meta-regression analyses indicated that GM volume deficits were influenced by greater overall levels of antipsychotics medication usage irrespective of antipsychotic agent grouping (Radua et al., 2012).

Cannabis use albeit not extensively investigated has been associated with alterations in regional brain volumes including LV enlargement (Rais et al., 2008), and volume reductions

longitudinally in the cannabinoid 1 (CB1) receptor enhanced areas of the thalamus (Welch et al., 2011), dorsolateral prefrontal cortex and cerebellum (Rais et al., 2010; Rapp et al., 2012).

1.5 Summary of the findings from longitudinal studies

There is a large evidence base for the presence of regional brain abnormalities in FEP including reduced global cerebral and hippocampal volume and LV enlargement (DeLisi et al., 1991; Cahn et al., 2002a; Kubicki, 2002; Pantelis et al., 2003; Steen et al., 2006; Morgan et al., 2007, 2010b; Dazzan et al., 2012; Haijma et al., 2013). There is also strong and increasing evidence for the longitudinal progression of these structural abnormalities (DeLisi et al., 1997; Wood et al., 2001, 2008; Lieberman et al., 2001; Cahn et al., 2002b, 2009; Pantelis et al., 2003; Velakoulis et al., 2006; Steen et al., 2006; van Haren et al., 2007, 2011; Nakamura et al., 2007; Borgwardt et al., 2008; Pol and Kahn, 2008; Sun et al., 2009; Kempton et al., 2010b; Walter et al., 2012), with this progression being more pronounced in the first few years of illness which then potentially tapers off (DeLisi et al., 1997; Pol and Kahn, 2008; van Haren et al., 2011). This may be less true in relation to LV enlargement, with on-going differential effects compared to healthy controls postulated to continue for up to 20 years after the FEP (Pol and Kahn, 2008; Kempton et al., 2010b). Several clinical factors may impact on regional brain volume abnormalities, including the administration of antipsychotic agents (Ho et al., 2011; Vita et al., 2012; Fusar-Poli et al., 2013), although inconsistent results have largely been demonstrated for any association with clinical factors to date (Cannon et al., 2015).

1.6 Structural MRI studies with QoL as an outcome

QoL and social functioning are key outcome measures in FEP. Improved QoL longitudinally has been associated with reduced psychotic and depressive symptoms (Thorup et al., 2010;

Gardsjord et al., 2016a; Oldis et al., 2016) as well as greater access to financial, housing and social supports. There have however been no structural MRI (sMRI) studies where QoL has been the outcome variable of interest.

1.7 Study aims and hypotheses

The study aims to determine clinical, sociodemographic and morphometric determinants of QoL 3 years after the onset of psychotic illness using a longitudinal study design.

1.7.1 Clinical hypotheses:

1. A shorter DUP will predict higher QoL scores at follow up.
2. Lower negative symptom scores and higher positive symptoms scores at baseline will predict higher QoL scores at follow up.
3. A baseline non-affective psychosis diagnosis will predict lower QoL scores at follow up.
4. A greater reduction in negative symptoms longitudinally will predict higher QoL scores at follow up.

1.7.2 Neuroimaging hypotheses:

1. Baseline brain measure reductions in GM, WM, hippocampal volume and LV enlargement and will predict lower QoL scores at follow up.
2. Progressive GM, WM and hippocampal volume reductions and LV enlargement will predict lower QoL at follow up.

Chapter 2

Methods

2.1 Study Design

This was a naturalistic longitudinal study of FEP patients examining if baseline regional brain morphometry measurements would be associated with QoL at 3-year follow up.

2.2 Participants

2.2.1 FEP participants

Patients were invited to participate in the initial FEP study if they met the inclusion/exclusion criteria and were receiving treatment in one of the following Health Services Executive (HSE) West areas of: West Galway Mental Health Services, East Galway Mental Health Services or Clare Mental Health Services. These areas had a combined catchment population of 342,617. In total, 45 individuals experiencing their first psychotic episode were recruited for the Galway First Episode Psychosis study between January 2007- December 2010 (Scanlon et al., 2014). The sample is not epidemiologically based as many potential participants declined the assessments or did not fulfil the inclusion criteria. The total number of patients identified for inclusion was not available from the initial study and no power calculation was carried out to select a specific recruitment target number of FEP patients.

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Maybe worth undertaking a power analysis from the literature – n query advisor is one I usually use but there are many others
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2.2.2 Healthy Control (HC) participant

Healthy controls (HCs) were recruited by advertisement in the local media in Galway, University Hospital Galway and the National University of Ireland, Galway. HCs were matched to patients for age and gender.

2.2.3 Inclusion criteria

Patients were included in the study if they:

1. Had been diagnosed as suffering a first episode of psychotic illness.
2. Had been administered less than 8 weeks of antipsychotic medication.
3. Being treated in one of the Health Services Executive (HSE) West areas described above.
4. Did not meet any exclusion criterion.

2.2.4 Exclusion Criteria

Exclusion criteria for the study consisted of:

1. Aged under 16 or over 55 years. Over the age of 55, age related MRI changes are considered to interfere with results.
2. A past history of a co-morbid alcohol or substance dependence disorder as defined by the DSM-IV or co-morbid axis 1 mental disorders (American Psychiatric Association, 1994).
3. A history of a neurological illness, learning disability or head injury resulting in loss of consciousness for more than 5 minutes.

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4. A history of oral steroid use in the three months prior to study participation or onset of psychosis.
5. The presence of any contraindication to MRI scanning (e.g. metallic implants) or any clinical relevant abnormality as adjudged by a neuroradiologist blind to participant diagnosis.

Additional HC exclusion criteria consisted of:

1. A personal history of a DSM-IV mental disorder.
2. A first degree relative with a history of a non-organic psychotic disorder.

2.3 Ethical Approval

The study was approved by the Clinical Research Ethics Committee, Galway University Hospitals. All patients over the age of 18 provided informed consent. Written parental consent was required for those participants under 18 years of age in addition to participant assent. Participants were compensated for any travelling expenses incurred. All scans were reviewed by a neuroradiologist and any abnormal radiological findings were forwarded to the patient's clinician for appropriate management.

2.4 FEP participant's clinical assessment at timepoint 1

FEP participants were interviewed using the Structured Clinical Interview for DSM IV (SCID-1) (First et al., 1997) to assess if they fulfilled diagnostic criteria for a psychotic disorder and to ascertain their appropriate DSM-IV axis 1 diagnosis relating to their psychosis. Interviews were conducted by JMF and HS. Both were trained on the SCID-1 and any doubt about the diagnosis or clinical presentation was discussed with the PI (CMD). Demographic details were attained through clinical interview which included details such as age, gender, relationship and employment status. The clinical data which was attained included information on age of onset of psychosis, and history of alcohol and psychoactive substance use. Medications history was also obtained including doses of previous and current psychotropic medications. Clinical notes, where relevant, were examined by psychiatrists affiliated with the research proposal (if informed consent was provided), to ascertain additional pertinent clinical data including any family history of a DSM-IV axis 1 mental disorder, duration of symptomatology and treatment attained.

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I would state that the interviewers underwent training with experienced clinicians (CMcD, JL) who had significant experience in conducting the SCID-1. In addition, where doubt was present in relation to patient diagnosis after the SCID-1 had been conducted, clinical notes read and patient clinician liaised with, a further discussion with the PI was undertaken to ensure certainty of diagnosis.

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2.5 HC assessments

HCs were clinically assessed and screened to exclude a lifetime history of any axis 1 disorder using the Structured Clinical Interview for DSM-IV – Non Patient Edition (SCID-NP) (First et al., 2002). Demographic and pertinent personal history details including age, gender, family history of mental illness, medication usage and alcohol and/or psycho-active substance use were also collected.

2.6 Structured clinical assessments

A number of validated clinical assessment scales were used in the study by trained clinicians or researchers.

2.6.1 Structured Clinical Interview for DSM-IV Research Version

As described above each individual was assessed using the Structured Clinical Interview for DSM-IV (SCID)- Patient Edition (First et al., 1997) a structured diagnostic interview used to determine DSM-IV Axis I disorders or the Structured Clinical Interview for DSM-IV – Non Patient Edition (SCID-NP) (First et al., 2002). Reliability kappa scores on the SCID vary from 0.79 for bipolar disorder to 0.94 for schizophrenia (Skre et al., 1991).

2.6.2 Global Assessment of Functioning

The Global Assessment of Functioning score (GAF) (Endicott et al., 1976) is a 100-point clinician-rated scale that measures an individual's overall level of psychological, social, and occupational functioning on a hypothetical continuum. Higher scores are associated with higher levels of functioning. Endicott et al. (1976) performed the first series of test-retest reliability studies on the GAF and found intra-class correlation coefficients (ICC's) ranging from 0.61 to 0.91.

2.6.3 The Beiser Scale

Duration of Untreated Psychosis (DUP) was measured for all FEP patients using the Beiser Scale (Beiser et al., 1993). DUP was defined as the interval between the first noted psychotic

symptoms and commencement of anti-psychotic medication. This is a semi-structured instrument and was conducted with the patient and their nominated close relatives (with their informed consent) to obtain information about the onset and development of symptoms and the early stages of treatment. Additional information was extracted from the participant's clinical records to verify timelines in relation to symptom development and treatment.

2.6.4 Positive and Negative Symptom Scale (PANSS)

All FEP participants underwent an assessment of symptomatology, using the PANSS (Kay et al., 1987) which is used for measuring symptom severity of patients with psychosis. Scores are given separately for the positive items, negative items, and general psychopathology. The PANSS has shown strong psychometric properties in terms of reliability, validity and sensitivity (Leucht et al., 2005). Patients were rated between 0 and 6 on thirty items. Measurement was based on clinical interview, collateral history from consented family members and/ or discussions with their current mental health care providers.

2.7 Neuroimaging Assessment: Brain Magnetic Resonance Imaging (MRI)

2.7.1 MRI scan procedures (both timepoints)

Prior to participating in an MRI brain scan, all participants were screened to ensure they had no contraindications to having an MRI scan. Contraindications for an MRI scan include the presence of metal implants or fragments anywhere in their body or a participant history of claustrophobia.

In relation to the MRI Brain scan itself, participants removed all metallic and magnetic objects prior to entering the Scanner suite. When prepared, participants were instructed to lie still in the MRI scanner and their head was padded on either side to assist with reducing motion artefact for the duration of the MRI brain scan. A birdcage head coil was placed over participant‘s heads prior to scan commencement to ensure homogeneity of acquired images. All participants were given earphones for hearing protection and were able to communicate verbally with the radiographer and/or researcher for the duration of the MRI brain scan (30 minutes) in case they required assistance. Furthermore, a buzzer was placed in the participants' hands, which could be pressed if any difficulties were being experienced during the MRI brain scan.

2.7.2 Structural MRI acquisition

High resolution MR data was acquired on a 1.5 Tesla Siemens Magnetom Symphony scanner (Erlangen, Germany) in the Department of Radiology, University Hospital Galway using a standard 4-channel head coil. Scans were carried out during scheduled evening and weekend research slots. For each individual, A standard localiser and T1-sagittal sequence was utilised to confirm the participants radiological position and placement of the image field-of-view to be in alignment with the anterior-posterior commissure (AC-PC) line.

Detailed high resolution contiguous axial slices parallel to this axis were acquired to give the best anatomical definition with the following sequences:

(i) Sequence 1 is a set of 3-Dimensional T1-weighted Magnetisation-prepared rapid gradient echo (MPRAGE) images. Field of View (FOV): 230mm, Relaxation time (TR): 1140ms, Echo Time (TE): 4.38ms, Inversion Time (TI): 600 ms, flip angle 15°. The matrix size was 256 x 256, interpolated to 512 x 512, yielding a pixel resolution of 0.45mm x 0.45mm with a slice thickness of 0.9mm.

(ii) Sequence 2 is a set of contiguous T2-weighted axial images with 5mm slice thickness, voxel size 1.0 X 0.5 X 5mm, echo time 95ms, repetition time 5070ms, and flip angle of 180°.

(iii) Sequence 3 is a set of contiguous T2-weighted fluid attenuated inversion recovery (FLAIR) images with 5mm slice thickness, voxel size 1.0 X 1.0 X 5.0mm, echo time 104ms, repetition time 8200ms, and flip angle of 180°.

Sequence 1 was used for computational neuroanatomical and region of interest morphometry analyses. Sequences 2 and 3 allowed for neuroradiological assessments of MRI scans. Participants received the identical MRI protocol at both baseline and at follow-up.

2.7.3 MRI image pre-processing

Pre-processing steps of MRI data were implemented in Matlab version 7.1. (MathWorks Inc., Natick, Massachusetts, USA) using Statistical Parametric Mapping (SPM5) (Wellcome Department of Imaging Neuroscience, London) (Friston et al., 2011). Due to magnetic field in-homogeneities (noise from scanner hardware, small movement artefacts etc.), MR images are not completely perfect visual representations. Hence, the images were converted from the standard MRI Digital Imaging and Communications in Medicine (DICOM) files into Medical Imaging NedCDF (MINC) format in order to correct for scanner-derived bias using N3 software, thereby making the voxels more homogenous (Sled et al., 1998). Images were then converted into NIfTI (Neuroimaging Informatics Technology Initiative) format for inclusion in subsequent analyses.

2.8 The longitudinal follow up of participants

All study participants were informed, when consenting for the initial baseline study, of the proposal for a follow-up assessment and a second MRI brain scan after approximately 3 years.

2.8.1 Participant re-recruitment at follow up

At 3-year follow up, all FEP and HC participants received written information in relation to the follow-up study and were given the option of withdrawing from the study at this juncture. Two weeks after receiving written information, participants were contacted by the researcher via a telephone call to ascertain their interest in completing one or both (clinical interview and MRI brain scan) aspects of the follow up study. Any persons expressed wish not to participate was respected and no further contact was made.

2.8.2 Clinical assessments at timepoint 2

Those who agreed to participate were re-assessed (by SMcI) using clinical screening procedures and interviewed using the SCID-1 or SCID-NP as appropriate to ascertain any appropriate DSM-IV axis 1 diagnosis that might be present and to ascertain which DSM-IV psychotic disorder FEP participants fulfilled at follow-up. All psychometric instruments (Section 2.5.5) were repeated at 3 year follow-up with both FEP and HC participants. In addition, two measures of QoL (the QLS and WHO-BREF), and the Hamilton Depression Rating Scale (HDRS), were completed by FEP participants and controls at follow up. An amended WHO Life Chart was completed by FEP participants alone.

2.8.2.1 Quality of Life Scale (QLS) - objective measure of QoL

The QLS is a clinician rated instrument, based on a semi-structured interview consisting of 21-items rated on fixed interval scales based up the clinician's judgement of the patients functioning in each of 21 areas. Each item is rated on a 0 to 6 scale; with higher scores reflect better QoL. The QLS takes approximately 45 minutes to complete and it is a well-validated scale with inter-rater reliability indices of 0.85- 0.97 reported (Heinrichs et al., 1984).

The QLS consists of 4 subscales:

1. Interpersonal Relations (8 items): This subscale measures aspects of interpersonal and social experience, such as relationships in the household where they reside and relationships with friends and acquaintances. There are also items related to social activity, social networks, social initiative, social withdrawal and sexual behaviour.
2. Intrapsychic Foundations (7 items): This subscale measures participants' sense of purpose, motivation, curiosity, anhedonia, aimless inactivity, empathy, and emotional interactions with others.
3. Instrumental Role (4 items): This subscale measures participants' occupational role, work functioning, current work level and work satisfaction.
4. Common Objects and Activities (2 items): This subscale measures participation over a two week period in relation to commonplace objects and activities including use of keys, a watch or use of public parks.

The QLS provides a total score, calculated as the sum of all subscale scores and this total score is used extensively throughout this thesis as a primary outcome measure of QoL.

2.8.2.2 WHOQoL-Bref Subjective QoL Measure

The WHOQoL-Bref (The World Health Organization- Bref) is a 28-item self-report questionnaire assessing QoL across four major domains: physical, psychological, social relationships and environment (WHO, 1998). It is an adapted form of the WHOQoL-100, and domain scores produced by the two instruments are highly correlated (r= 0.9) (The WHOQOL Group, 1998). Individual items within each domain are scored on a 5-point Likert scale (0-4) with higher scores indicating a higher QoL. Unlike the QLS, a total score cannot be attained by summing the scores of the four domains.

2.8.2.3 Hamilton Depression Rating Scale (HDRS)

The 17-item HDRS objectively rated scale was utilised to ascertain depressive symptomatology. The HDRS measures symptoms of depression experienced over the past week (Hamilton, 1960). Depressive symptoms are measured within a 0-50 point range, with 8 item rated on a 5-point scale (0-4) and nine items rated on a 3-point scale (0-2), with higher scores indicating greater severity. The HDRS takes approximately 15-20 minutes to complete. The HDRS has been demonstrated to be a valid and reliable measure of both the presence and severity of depression (Williams, 1988).

2.8.2.4 The WHO LIFE Chart

Information on illness course was obtained using an amended version of the WHO Life Chart (Harrison et al., 2001). This measure has been used successfully in previous long-term follow-up psychosis studies, and has been shown good reliability indices (Susser et al., 2000). At follow-up, extensive information (e.g. clinical, social and service use) was obtained from interview with participants, and where consent was attained, from examination of clinical records and interviews with treating clinicians and / or consented family members.

2.8.3 Repeat MRI brain scanning

Of the 32 FEP participants assessed and scanned at baseline, 29 agreed to repeat MRI brain scanning. 17 HCs agreed to follow up but repeat MRI brain scan was only obtained on 12 HCs. FEP and HC participants were scanned using an identical MRI protocol to that used at baseline (see section 3.5.1). The three FEP participants who declined repeat MRI brain scanning were agreeable to repeat clinical assessments.

2.9 Statistical analysis

All analyses were conducted using Statistical Package for the Social Science (SPSS) version 23.0 for windows (IBM SPSS Corp., Armonk, New York 2015).

2.9.1 Data analysis

Means and standard deviations (SDs) were attained for all appropriate demographic, clinical and neuroimaging variables. Baseline and follow-up mean values for selected demographic, clinical and neuroimaging variables for FEP participants were compared by conducting paired t-tests. Bivariate correlations (Pearson r) were examined between QLS total score and psychiatric symptoms at baseline and follow up. Significance level was set at the 0.05 level.

2.9.2 Linear regression

To identify independent baseline predictors of QoL at follow up, linear regression modelling was used, with the R^2 statistic indicating the magnitude of the relationship between the independent and the dependent variable. The independent variables consisted of demographic variables; age, gender as well as clinical variables; DUP, PANSS-negative symptoms, PANSS-positive symptoms and diagnosis (characterized as either affective or non-affective psychosis).

While medication usage and substance misuse are variables to consider in an analysis of QoL in psychosis, they were not selected as independent variables of interest in this study. Medication non-compliance was not assessed in the baseline or longitudinal study. Linear regression models were also used to identify if any of these baseline variables or their change variables (timepoint 1 minus timepoint 2) predicted QLS at the 3 year follow-up period. Therefore, in addition to the baseline variables, change in PANSS-negative symptoms, PANSS-positive symptoms and diagnosis (characterized as either affective or non-affective psychosis) over the 3 year follow up period were included in the regression analysis.

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Hi Shane – I think you need a rationale for not including – very low rates of medication non-adherence due to their living environment and that medications were dispensed.

Cannabis use - ~ 25% so worth considering a yes / no dichotomous and examining

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2.9.3 sMRI processing and statistical analysis

Regional volumetric estimates of LV volume, GM and WM tissue volumes were extracted for analysis using Freesurfer (Fischl et al., 2002). Hippocampus volume was segmented manually by trained raters who were blinded to diagnosis and according to a strict anatomical protocol using ITKsnap software (Yushkevich et al., 2006). Similar linear regression analyses to what was outlined above were carried out to identify morphometric associations of QoL, with age, gender and intracranial volume (ICV) (for measures of volume only) included as co-variates.

Chapter 3

Quality of Life in FEP

Results

3.1 Participant characteristics

3.1.1 Sociodemographic and clinical characteristics of participants

During the study period between January 2007 and December 2010, 45 patients were enrolled in the Galway First Episode Psychosis study. Of these, 32 (71%) completed follow-up assessments 3 years later. Efforts were made to contact all initial participants for the follow up study. including telephone, email and a letter inviting them to participate. Their wish not to participate was respected if they declined, with no further contact being made.

There were no statistically significant differences between completers and non-completers on any demographic or clinical variables (Table 3.1). In terms of the 32 FEP patients, they had a mean of 16 years (SD 2.5) of education at baseline, 10 (31.3%) were married or were in a relationship and 21 (65.6%) had employment. Eight individuals (25%) engaged in psycho-active substance misuse (cannabis) at baseline. However, only one individual (3.1%) continued to use psycho-active substances at follow-up. The cumulative dose of medication (in CPZ equivalents) was 4937mg (SD = 6820) at baseline. Twenty-two (68%) FEP patients required admission at baseline with 6 individuals (27.7%) being detained under the MHA 2001 (involuntary patients) at this time. The mean DUP was 13.6 months (SD = 10.2). The median DUP was 7 months. The clinical characteristics of participants is summarised in Table 3.1. FEP participant baseline and follow up brain volumes are displayed in mean (SD). Paired t-test analysis is conducted between baseline and follow up on the clinical and brain imaging variables for study completers.

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Start with letter requesting participation before mentioning telephoning participants
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Were participants aware they might be contacted again
If so – it would be fine to telephone / email etc
If not – a letter first would be the norm

In writing this paragraph – put letter before email / telephone

3.1.2 Psychometric instruments

In relation to clinical data, FEP participants demonstrated significant improvements in total, positive, negative and general psychopathology symptoms as measured on the PANSS at 3-year follow-up ($p < 0.01$). Similarly, GAF scores demonstrated significant differences between baseline and follow up ($p<0.05$).

Table 3.1 Clinical characteristics of participants

	Baseline				3 year Follow-Up	
	Total FEP (N=45)	**HC (n=23)**	**FEP (n=32) Study completers**	**FEP (n=13) Study non-completers**	**HC (n=17)**	**FEP (n=32) Study completers**
	n (%)		**n (%)**	**n (%)**	**n (%)**	**n (%)**
Male Gender	30 (66.7)	15 (65.2)	20 (62.5)	10 (76.9)	9 (52.9)	20 (62.5)
	Mean (SD) {Range}		**Mean (SD) {Range}**	**Mean (SD) {Range}**	**Mean (SD) {Range}**	**Mean (SD) {Range}**
Age	28.1 (8.3) {16-50}	30.7(8.3) {18-47}	28.4 (8.9) {17-50}	28.4 (8.9) {17-50}	32.8 (8.13) {21-46}	31.4 (8.9) {19-53}
PANSS-						
Total	65.6 (13.9)	-	66.6 (13.2)	64.1 (16.7)	-	43.1 (12.5)**
Positive	17.4 (4.1)	-	17.8 (4.4)	16.2 (3.0)	-	9.5 (3.2) **
Negative	15.3 (6.3)	-	15.1 (6.0)	16.1 (7.1)	-	11.3 (5.6) **
General	33.2 (7.3)	-	33.7 (7.0)	31.8 (8.3)	-	22.3 (5.6)**
GAF	51.3 (10.9)	-	51.1 (11.7)	51.9 (9.1)	91.3 (8.1)	75.6 (14.2)*
QLS						
Total	-	-	-	-	117.3(6.9)	98.9 (21.2)
QLS-I	-	-	-	-	43.4 (4.5)	35.4 (10.4)
QLS-II	-	-	-	-	21.9 (2.3)	18.2 (6.1)
QLS-III	-	-	-	-	39.9 (2.4)	34.2 (7.0)
QLS-IV	-	-	-	-	12.0 (0)	11.1 (1.3)
BREF						
Physical	-	-	-	-	88.2(12.9)	69.8 (15.4)
Psychological	-	-	-	-	79.5(10.8)	58.5 (18.7)
Social	-	--	-	-	79.2 (16.7)	55.4 (23.1)
Environmental	-	-	-	-	82.8 (10.3)	69.4 (16.4)
Brain Regions:						
Left LV ($mm^{3)}$	8640.7(3617.4)	-	-	-	-	9445.9 (4193.3)*
Right LV (mm^3)	8142.0 (4352.4)	-	-	-	-	8914.1(4785.2)*
Left Hipp. (mm^3)	2792.3 (351.2)	-	-	-	-	2887.6(367.84)
Right Hipp. (mm^3)	2808.48 (375.2)	-	-	-	-	2833.59 (328.9)
GM (cm^3)	677.41 (51.4)	-	-	-	-	664.68 (54.8)*
WM (cm^3)	503.70 (48.7)	-	-	-	-	493.04 (47.9)*

FEP baseline completers vs FEP follow up completers *p<0.05; **p < 0.01 level.

Abbreviations: BREF= WHO-BREF sQoL Scale; FEP= First Episode of Psychosis; GAF=Global Assessment of Functioning; GM = Grey Matter; Hipp. = Hippocampus; LV = Lateral Ventricles; WM= White Matter; QLS= Quality of Life Scale; QLS I. =Interpersonal Relations; QLSII. =Instrumental Role; QLS III. =Intrapsychic Foundations; QLSIV. =Common Objects and Activities; PANSS=Positive and Negative Symptom Scale; SD=Standard Deviation.

3.1.3 Diagnostic Stability

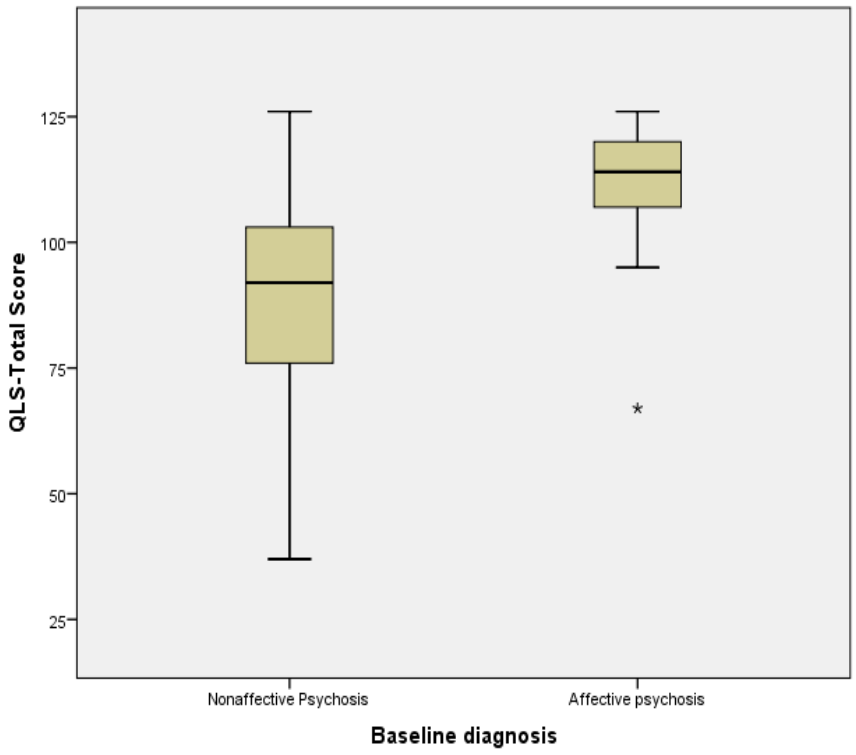
Considerable diagnostic instability was noted, albeit this was predominantly within sub-group of affective and non-affective psychosis, with only one individual switching from an affective psychosis to a non-affective psychosis at follow up (see Table 3.2). The presence of a non-affective (compared to an affective) psychosis at baseline was demonstrated to be associated with a lower QoL as measured by the QLS at 3-year follow up ($F = 1.7$, $p = 0.005$) (Figure 3.1). Removal or inclusion of an outlier in the affective psychosis group did not affect statistical significance.

Table 3.2 FEP patients diagnosis at baseline and follow up

Diagnostic Status	**Baseline N (%)**	**Follow Up N (%)**
Non-Affective Psychosis	18 (56.3)	19 (59.4)
Schizophrenia	4 (12.5)	11 (34.4)
Schizoaffective disorder	1 (3.1)	3 (9.4)
Schizophreniform disorder	7 (21.9)	0 (0.0)
Delusional disorder	2 (6.2)	1 (3.1)
Psychosis NOS	4 (12.5)	3 (9.4)
Substance Induced PD	0 (0.0)	1 (3.1)
Affective Psychosis	14 (43.7)	13 (40.6)
Mania	10 (31.3)	9 (28.1)
MDD	4 (12.5)	4 (12.5)

Abbreviations: NOS= Not Otherwise Specified; PD= Psychotic Disorder; MDD= Major Depressive Disorder.

Figure 3.1 Boxplot of Baseline Diagnosis and QOL Score at Follow Up



3.1.4 QoL instruments

As previously described in sections 2.8.2.1 and 2.8.2.2, there were two QoL measures in this study, QLS-objective measure and the WHOQoL Bref- subjective QoL measure. Both oQoL and sQoL assessments were completed by the FEP patients that were followed up. Table 3.3 shows the extent of the correlations between each of the subscales in each scale. Those oQoL and sQoL subscales that correlated highly with each other included that between QLS I (interpersonal Relations) and BREF Social (r=0.60). This is to be expected as QLS I and BREF

social involve similar items such as close relationships with immediate family or friends. Other oQoL and sQoL sub-scales had a minimal correlation with each other, including the correlation between QLS IV (common objects) and BREF physical (r=0.16). The BREF physical subscale covers aspects of activities of daily living, mobility and sleep while the common objects subscale incorporates items encompassing participation in certain activities such as shopping and attending social events.

Overall Table 3.3 reflects the fact that QoL scales can discriminate between various aspects of life functioning in validated scales. While both QLS and the BREF scales were obtained, it was Total QLS score that was selected as the dependant variable for the analysis of QoL in this thesis. The QLS scale provides a total score, unlike the BREF, and encompasses various aspects of life functioning. Less statistical power is lost in including total QLS score as the dependent variable in regression analyses rather than 4 subscales of the BREF. Furthermore, the QLS is a widely used instrument in the field of psychosis research (McGorry et al., 2008).

Table 3.3 Correlations between the WHO-BREF and QLS- QoL Scales

	BREF 1	**BREF 2**	**BREF 3**	**BREF 4**	**QLS-Total**	**QLS-I**	**QLS-II**	**QLS-III**	**QLS-IV**
BREF –Physical (1)	1	0.76**	0.54**	0.78**	0.48**	0.38*	0.34	0.56**	0.16
BREF –Psychological (2)	0.76**	1	0.54**	0.64**	0.45*	0.36*	0.35*	0.48**	0.25
BREF –Social (3)	0.54**	0.54**	1	0.58**	0.56**	0.60**	0.13	0.59**	0.52
BREF-Environmental (4)	0.78**	0.64**	0.58**	1	0.39*	0.36*	0.20	0.45**	0.17
QLS-Total	0.48**	0.45*	0.56**	0.39*	1	0.93**	0.72**	0.91**	0.62
QLS-I	0.38*	0.36*	0.60**	0.36*	0.93**	1	0.51**	0.79**	0.61
QLS-II	0.34	0.35*	0.13	0.20	0.72**	0.51**	1	0.53**	0.21
QLS-III	0.56**	0.48**	0.59**	0.45**	0.91**	0.79**	0.53**	1	0.59
QLS-IV	0.16	0.25	0.52**	0.17	0.62**	0.61**	0.21	0.59*	1

Abbreviations: BREF= WHO-BREF sQOL Scale; QLS= Quality of Life Scale; QLS I. =Interpersonal Relations; QLSII. =Instrumental Role; QLS III. =Intrapsychic Foundations; QLSIV. =Common Objects and Activities. * $p < 0.05$ level; **$p < 0.01$ level.

3.2 Examination of clinical factors at baseline as predictors of QoL at follow up

3.2.1 Findings of baseline clinical assessment and QoL

Linear regression analysis was conducted where the dependent variable was QoL (QLS Total score) and the independent variables were; gender, age, DUP, positive symptoms, negative symptoms and diagnosis (characterized as either affective or non-affective psychosis) (Table 3.4). This model represents 29% of the variance (R^2=0.29, Standard Error of the Estimate {SEE} = 19.9, F = 1.74, $p < 0.15$). While there were no statistically significant findings, baseline

diagnosis (the presence of an affective psychosis) had a trend towards significantly predicting higher QoL at follow up.

Table 3.4 Baseline clinical predictors of QLS at follow up

Independent Variables	B (SE)	t	p
Gender	6.90 (8.91)	0.77	0.45
Age	-0.36 (0.43)	-0.86	0.40
DUP	0.04 (0.23)	0.193	0.85
Positive symptoms	-0.70 (0.83)	-0.84	0.41
Negative symptoms	-0.03 (0.69)	-0.04	0.97
Baseline diagnosis*	16.77 (8.84)	1.90	0.07

* Affective compared to non-affective psychosis. B = Unstandardised co-efficient; DUP = Duration of Untreated Psychosis; PANSS = Positive and Negative Syndrome Scale; SE = Standard Error

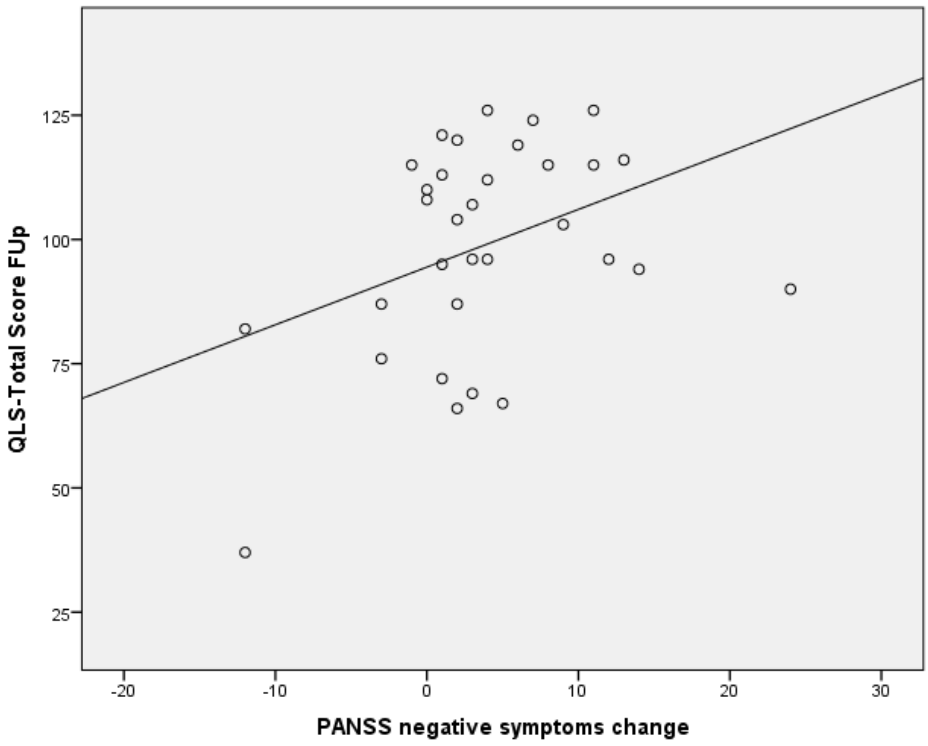
3.2.2 Longitudinal clinical findings and QoL

Linear regression analysis was performed to investigate the predictive value of baseline and change clinical variables on QoL. In this model, QLS Total score was the dependent variable and the independent variables were; age, gender, change in negative symptoms, change in positive symptoms, negative and positive symptoms at baseline and diagnosis at 3 year follow-up. This model represents 61% of the variance ($R^2 = 0.61$, SEE = 15.5, $F = 4.4$, $p < 0.002$) (Table 3.5).

In this analysis, higher negative symptom score at baseline (B = -1.82, SE = 0.79, $p < 0.03$) was predictive of lower QoL at follow-up while a greater reduction in negative symptoms over time (B= 2.00, SE = 0.62, $p < 0.004$) was predictive of higher QoL at follow-up. Diagnosis (affective/non-affective psychosis), age, gender or positive symptoms demonstrated no significant predictive value.

The relationship between change in negative symptoms from baseline to follow up and quality of life scores at follow up is displayed in Fig 3.2.

Figure 3.2 Scatterplot representing PANSS negative symptoms change* in relation to QoL



*Negative Symptoms change= Timepoint 1- Timepoint 2, (r = 0.38, P=0.05)

Table 3.5 Baseline and change predictors of QLS at follow up

Independent Variables	**B (SE)**	**t**	**p**
Gender	1.96 (7.04)	0.28	0.78
Age	-0.14 (0.37)	-0.41	0.68
DUP	0.04 (0.18)	0.20	0.85
Positive symptoms baseline	-1.76 (1.24)	-1.41	0.17
Negative symptoms baseline	-1.82 (0.79)	-2.27	**0.03**
Diagnosis at 3 year follow-up*	9.26 (7.22)	1.56	0.21
Positive symptoms change**	1.48 (0.95)	3.21	0.13
Negative symptoms change**	2.00 (0.62)	1.28	**0.004**

* Affective compared to non-affective psychosis.

**Symptoms change= Timepoint 1-Timepoint 2.

B = Unstandardised co-efficient; DUP = Duration of Untreated Psychosis; PANSS = Positive and Negative Syndrome Scale; SE = Standard Error.

3.2.3 Regional brain volumes and QoL

Linear regression analysis was conducted to examine if baseline regional brain variables were predictive of QoL (QLS=dependent variable); the various brain regions as independent variables controlling for age, gender and ICV (intra-cranial volume) (Table 3.1). None of the baseline brain regional volumes predicted QLS score at follow-up (Table 3.7).

Table 3.6 Baseline neuroimaging as predictors of QoL

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Variable	R^2	F (p)	B (SE)	t	p
Left LV	0.49	4.9 (0.001)	0.002 (0.001)	1.72	0.10
Right LV	0.44	3.9 (0.08)	0.001 (0.001)	0.12	0.47
Left Hippocampus	0.28	2.6 (0.06)	0.002 (0.010)	0.24	0.86
Right Hippocampus	0.28	2.6 (0.06)	0.100 (0.260)	0.26	0.80
GM	0.35	-3.5 (0.01)	0.001 (0.001)	-1.67	0.11
WM	0.53	2.5 (0.001)	0.001 (0.001)	0.02	0.98

Abbreviations: GM= Grey Matter; LV = Lateral Ventricles; WM = White Matter

3.2.4 Longitudinal imaging assessment as predictors of QoL

To study longitudinal effects, a linear regression model analysis was performed to investigate the predictive value of baseline and change independent variables on QoL. In this model, QLS total score was the dependent variable. The independent variables included baseline volumes and changes in volume over time of bilateral LVs, bilateral hippocampus, WM and GM,

controlling for age, gender and ICV (Table 3.8). Enlargement of the left LV volume was significantly (B = 0.006, SE = 0.002, p = 0.03) associated with reduced QoL (Fig. 3).

Table 3.7 Brain volume change* values from baseline to follow up as predictors of QoL

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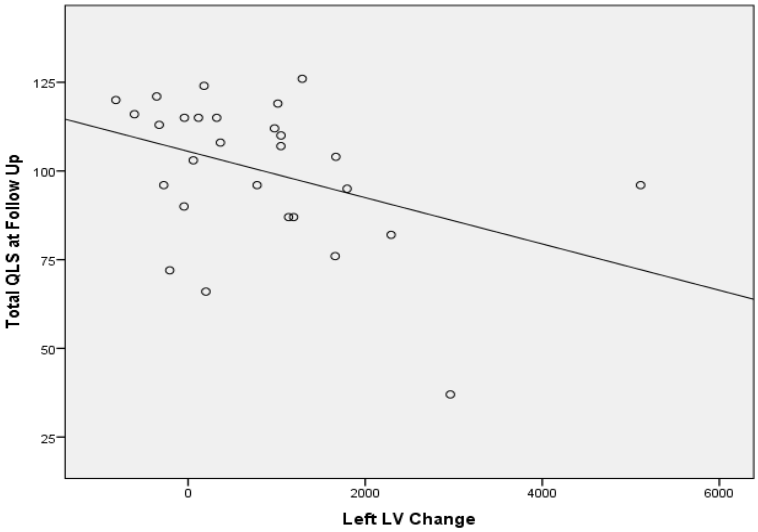
Variable	R^2	F (p)	B (SE)	t	p
Left LV Change	0.64	6.2 (0.001)	-0.006 (0.002)	-2.29	**0.03**
Right LV Change	0.55	4.4 (0.005)	-0.005 (0.003)	-1.78	0.09
Left Hippocampal Change	0.15	0.77 (0.59)	-0.001 (0.012)	-0.09	0.92
Right Hippocampal Change	0.18	0.93 (0.49)	0.01 (0.015)	0.77	0.45
GM Change	0.36	2.4 (0.0002)	-0.001 (0.001)	-1.05	0.25
WM Change	0.25	1.4 (0.025)	0.0001 (0.001)	-0.14	0.89

*Change= Timepoint 1- Timepoint 2

Figure 3.3 Scatterplot of change in left LV volume (mm^3) and QoL at Follow Up



(r= -0.40, p=0.04)

Chapter 4

QoL in FEP

Discussion

4.1 Summary of main findings of FEP Study

In this FEP cohort, there was a statistically significant improvement in positive, negative, general and total PANSS scores at 3-year follow up. In bivariate analysis, individuals with a diagnosis of non-affective psychosis had a significantly lower QLS score. Although in linear regression analysis the presence of a non-affective psychotic disorder at baseline was associated at statistical trend level with QoL at 3-year follow up, other clinical measures hypothesised such as baseline positive or negative symptoms or DUP were not significantly associated with QoL. When changes in clinical variables over time were examined, the only significant finding related to a reduction in negative symptoms associated with a higher QoL. Some diagnostic instability was noted, though this was predominantly within the sub-groups of affective and non-affective psychosis, with only one individual switching from an affective psychosis to a non-affective psychosis. It could be expected that progressive brain volume loss would be associated with clinical and functional outcome decline following a FEP (Roiz-Santiáñez et al., 2013).

Baseline neuroimaging variables did not predict QoL at 3-year follow-up. However, when change in regional brain volumes was examined, left LV enlargement was inversely associated with QoL. Over the 3-year follow-up period, statistically significant reductions in GM and WM volumes and increases in LV volume were noted. When change in regional brain volumes was examined, only left LV enlargement was inversely associated with QoL. LV enlargement longitudinally was found to be negatively associated with QoL. This is one of the most replicated findings within neuroimaging in psychosis (Steen et al., 2006; Cahn et al., 2009; Kempton et al., 2010a) and some studies have reported that those with more chronic psychotic illness have greater impact structurally in this brain region than earlier in the course of illness (Kempton et al., 2010a; Fusar-Poli et al., 2013). This LV enlargement finding would need to be further replicated in larger samples in order to further assess its viability as being a clinically relevant biomarker. A biomarker is a characteristic that is objectively measured and evaluated

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I am not sure what this means ~ progressive enlargement of the LV has been demonstrated with illness course in several previous studies

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Larger studies have also demonstrated this
Given the results of this study and others demonstrating progressive LLV enlargement (REFS), it could be postulated that progressive LLV may be a potential biomarker for neuroprogressive changes in the brain in psychosis.
However, there are a number of confounding variables including xxx

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as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention (Atkinson et al., 2001). Brain imaging may be more useful as a dimensional marker rather than a diagnostic marker (Hager and Keshavan, 2015) and LV change over time may be useful as a research tool to measure neuroprogressive processes in the brain that are manifest through this imaging measurement. On the other hand, clinical measures such as progression in negative symptoms are more likely to have more clinical utility as an individual prognostic measure in the short-term. Clinical markers are also more easily implemented, more affordable and less intrusive than imaging or other biomarker investigations. The LV enlargement finding must also be contextualized as being confounded by other factors such as medication usage (Ho et al., 2011) and negative symptoms (Chang et al., 2011).

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Whilst LLV enlargement may indeed be a biomarker for neuroprogression in psychosis, the clinical utility of other potential biomarkers attained from clinical or psychometric evaluation would be greater…

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A 25 minute scan v 2 hours of psychometric evaluation

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4.2 Discussion of clinical findings

QoL at follow-up was not predicted by baseline positive or negative symptoms or DUP, thus the first two clinical hypotheses were rejected. The third hypothesis, that baseline non-affective psychosis diagnosis would be predictive of QoL at follow-up, was supported, although this did not reach statistical significance in the multivariate analysis. In keeping with the fourth hypothesis, a greater reduction in negative symptoms over time was associated with QoL at follow-up. Changes in positive symptoms were however not predictive of QoL at follow up.

Consistent with other long-term studies, there was considerable stability with respect to diagnostic stability, with only one person having a diagnostic change; from an affective to a non-affective psychosis. One study identified stability of schizophrenia as being up to 85% at 12-26 year follow up (Morgan et al., 2010a). Factors found to be associated with associated with a diagnostic change to schizophrenia include living alone being single, socially isolated and black African in large urban areas as well as clinical factors such as having a longer DUP,

suffering symptoms of reality distortion and negative symptoms (Heslin et al., 2015). In a relatively small and Caucasian population such as this current cohort, it is likely that from a clinical standpoint, negative symptoms had a considerable part to play in the diagnostic stability of our patient sample.

4.3 Negative symptoms and QoL

Negative symptoms involve impairment of normal affect and emotion, deficits that were recognized and described by the earliest scholars of schizophrenia as the key, fundamental symptoms of the disorder (Andreasen, 1997). For example, Emil Kraepelin described schizophrenia as "a weakening to those emotional activities, which permanently form the mainsprings of volition". Similarly, Eugen Bleuler's fundamental symptoms of schizophrenia included loss of the continuity of associations, loss of affective responsiveness, loss of volition, ambivalence, and autism. More recently, at the 2005 National Institute of Mental Health supported consensus meeting, schizophrenia experts from across the world agreed that negative symptoms are a distinct domain of schizophrenia. They also supported five sub-domains of symptoms: 1) alogia, 2) blunted affect, 3) asociality, 4) anhedonia, and 5) avolition (Stahl and Buckley, 2007). It can thus reasonably be stated that negative symptoms, more so than positive symptoms (delusions and hallucinations) represent the core deficit of schizophrenia (Andreasen, 1997). Hughlings Jackson was the first to describe positive and negative symptoms (Ho et al., 1998). Various clinical factors have previously been associated with an increased risk of negative symptoms including male gender, a family history of non-affective psychosis, poor pre-morbid adjustment, and depressive symptoms at illness onset (Gee et al., 2016), with resultant adverse effects on social and vocational functioning.

The presence of negative symptoms have consistently been associated with reduced functionality, both in a vocational and social context (Blanchard et al., 1998; Ho et al., 1998; Bowie et al., 2006; Rosenheck et al., 2006). Fervaha and colleagues (2014) found that negative symptoms explained a large portion of the variance in functional status, even after the variance ascribed to other clinical variables including positive symptoms, depression, anxiety and extrapyramidal symptoms were statistically accounted for (Fervaha et al., 2014). Similarly in FEP, the presence of negative symptoms has been demonstrated to have a negative predictive value in relation to future global functioning (Peña et al., 2012).

Although there is a paucity of studies examining clinical variables and how they might predict QoL at follow-up, negative symptoms have previously been identified as having predictive value for QoL in established psychosis, with two studies demonstrating that baseline negative symptoms had greater predictive value of poor QoL at two-year follow up compared to positive symptoms in schizophrenia (Ho et al., 1998; Thorup et al., 2010). In addition, Chugh and colleagues observed that negative symptoms are predictive of a number of QoL factors including physical and psychological well-being, with a greater predictive value compared to positive or general psychopathology symptoms (Chugh et al., 2013). These studies, in addition to the findings from this study, suggest that the severity of negative symptoms at baseline, and the ongoing presence of negative symptoms, have significant deleterious effects on both functioning and QoL. This study, in addition to longitudinal data from other researchers (Ho et al., 1998; Thorup et al., 2010), highlight the importance of assessing QoL in FEP individuals and its importance as an outcome measure. Saville and colleagues found that it was experiential deficits with respect to negative symptoms rather than expressive factors that were associated with sQoL, suggesting that PANSS assessment of negative symptomatology may not be sufficient to address subjective elements associated with QoL (Savill et al., 2016).

The College of Psychiatrists of Ireland's draft proposal suggests that all Early Intervention services for Psychosis should include assessment of "Functional outcomes" which would include measures of social and occupational functioning and QoL. These assessments would occur 12 months after the detection of a FEP. The DETECT services in South County Dublin, presently

assess QoL at 12 months after enrolment in their Early Intervention Psychosis programme (Client Wisconsin Quality of Life Client Questionnaire). An increasing awareness of the aspects of QoL and efforts at targeting negative symptoms early in a patients' psychotic illness, could not alone improve symptomatology, but also have a long-lasting positive impact on functioning and QoL.

4.4 Neuroanatomical Discussion

As discussed in the introduction chapter (Sections 1.4.3 and 1.4.4), structural brain abnormalities both at FEP and longitudinally after a FEP have been demonstrated. The most consistent of these brain structural abnormalities relate to LV enlargement (Vita et al., 2006, 2012; Fusar-Poli et al., 2013), hippocampal (Wright et al., 2000; Vita et al., 2006) and global cerebral volume reduction (Wright et al., 2000; Vita et al., 2006, 2012; Fusar-Poli et al., 2013). Progressive enlargement of LVs (Steen et al., 2006; Cahn et al., 2009), and progressive reduction in total GM (Steen et al., 2006; Zipparo et al., 2008; Gutierrez-Galve et al., 2015), and total WM (De Peri et al., 2012) have been reported; although such findings are not universally identified (Schaufelberger et al., 2011; Haukvik et al., 2016).

Contrary to the neuroimaging hypotheses of the study, baseline brain measures of GM, WM, hippocampal volume and LV were not predictive of lower QoL scores at follow up. With respect to the change in brain regions over time; GM, WM, hippocampus volume reductions and progressive right LV enlargement were not predictive of lower QoL at follow up as had been hypothesised. However progressive left LV enlargement predicted lower QoL at follow up. This finding is consistent with a recent study examining global functioning over a 14 month period (Del Re et al., 2015), where LV enlargement predicted lower global functioning. Similarly, poorer functioning has been associated with enlarged LV (Cahn et al., 2002a; Nakamura et al., 2007) and reduced GM over time (Cahn et al., 2002a).

At present, despite the relative consistency of identifying LV enlargement in both FEP and chronic psychosis, further work is required to identify if progressive LV enlargement is consistently predictive of functional outcomes and QoL. Replication of our study findings in a larger cohort with allowance for a range of confounds (e.g. different psychotic diagnoses, pre-morbid functioning, IQ) would further elucidate if progressive LV enlargement could be a potential biomarker for QoL and functioning in psychosis. Despite the relative expense of neuroimaging investigations, given advances in personalized medicine, brain imaging biomarkers could potentially be utilised in the future to assist in the individual management of patients with FEP by guiding therapeutic options and prognostic predictions. Based on these findings, the potential benefit of pharmacological and psychosocial interventions in individuals who present with significant negative symptoms and who demonstrate progressive LV enlargement should be further explored.

4.5 Strengths and limitations of the study

Particular strengths of this study include a relatively representative sample of FEP patients recruited from different mental health services covering a large catchment area in the West of Ireland. The sample included subjects from both genders and with a wide age range. Participants were followed up for a considerable period of time (an average of 3 years approximately) with a modest drop-out rate and were well-validated psychometric instruments by experienced researchers. Follow-up assessments of participants were comprehensive and comprised multifaceted validated structured assessments of clinical and functional impairment. The study utilized robust MRI analysis techniques to quantitatively measure regional brain volume changes over time.

As this is the first study to date to examine the association between baseline neuroimaging variables and QoL in a FEP sample, findings are thus preliminary and require replication. Study

limitations include the fact that this was a clinically heterogeneous FEP cohort, with for example only 34% having a diagnosis of schizophrenia at follow up, and a modest sample size which and thus may not have had the statistical power to detect other significant findings. No QoL data was collected at baseline, and more detailed clinical and imaging variables could have been assessed.

4.6 Future work on this cohort

Given that certain clinical and structural brain regions at baseline, or changes in these variables over time were predictive of QoL at 3-year follow up, further longitudinal evaluations at 5 and 10 year follow-up of these and other hypothesised variables could be undertaken to assess if these progressive effects persist or vary over time. In addition, the use of other neuroimaging techniques such as Diffusion Tensor Imaging (DTI) (obtained for some study participants) could be undertaken to allow an examination of the integrity of white matter anatomy over time in individuals with FEP and ascertain how this relates to a range of clinical factors including QoL.

4.7 Conclusion

This study demonstrated that patients who 3 years after their first episode of psychosis display increasing negative symptoms and lateral ventricular enlargement also manifest lower QoL. The study indicates that the trajectory of these measures of negative symptoms and LV volume enlargement over time is a better predictor of poor QoL than cross-sectional measures, and likely reflect a neuroprogressive process discernible in brain morphometry and externally manifest in symptomatology and poor outcome in at least some patients after their FEP. Such longitudinal clinical and neuroanatomical measures represent potential quantitative biomarkers for research studies attempting to identify interventions to ameliorate this neuroprogressive process.

Chapter 5

QoL in long-stay patients transferred into the community

Introduction and Methods

5.1 Introduction

This study sought to evaluate the QoL and social functioning of former long-stay psychiatric patients who were transferred from a large institutionalised hospital into community residences. “Long-stay” is a term used to define those residing in a hospitalized setting for greater than one year (Leff and Trieman, 2000). All included patients (see Table 6.1) had either previously been unsuccessfully discharged or required a supportive community placement that was unavailable to them prior to hospital closure.

The Clare Mental Health Service was one of the first mental health services within the Western region of Ireland to close its institution in 2001 (Our Lady's Hospital, Ennis) with other institutions closing over the course of the following 10 years (Mental Health Commission and Annual Report, 2011). The study cohort resided in designated rehabilitation hospital wards but no formal rehabilitation program was implemented prior to their community transfer.

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The community transfer options available after hospital closure included residing in low, medium or high support hostel accommodation or transfer into their own residence with regular community mental health support. Low support hostel refers to a residence where patients live largely independently and where a support worker calls in weekly to check those living there are stable. Medium support hostels refer to residences where there is a nurse overnight and high support refers to daily nursing and support staff on site 24 hours.

The word "transfer" is used rather than discharge as these patients remained patients of the Clare Mental Health Services, irrespective of their Mental Treatment Act 1945 status (voluntary or involuntary patients). The transition to community care required significant planning and consideration of the patients' links to local community supports where they may have had family or friends prior to their hospitalisation and their own multi-faceted care requirements.

This study was undertaken in order to document and assess longitudinally, the progress of this chronic cohort of long-stay patients as they underwent a significant milestone of change in their

living circumstances. Consideration was given to similar studies taking place within the UK where guidance as to assessment selection was taken (Leff et al., 1994).

5.1.1 Long-stay psychiatric institutionalised patients

Long-stay psychiatric institutionalised patients have been defined as those patients suffering severe and enduring mental illness with both active symptomatology and impaired social functioning as a consequence of their mental illness (Wykes and Holloway, 2000). The care requirements of this patient cohort are often multi-faceted and encompass physical, social and psychological needs. Transfer out of a residential to a community setting is a significant life event for patients and its effect on QoL and social functioning is important to understand. Internationally, there have been efforts to longitudinally assess these patients (Leff and Trieman, 2000; Lesage et al., 2000; Priebe et al., 2002; Grinshpoon et al., 2006; Ryu et al., 2006; McInerney et al., 2010; Petersen et al., 2013), although further studies are needed to examine factors associated with successful community transfer. Furthermore, attaining a good understanding of the challenges encountered can provide evidence on how best to support this cohort of patients when they are being transferred out of residential units.

5.1.2 Development of Community Psychiatry internationally

The process of deinstitutionalization with an associated closure of the large institutional hospitals and transfer of patients into the community began in the 1960s. It occurred on a background of developments in antipsychotic medications, a greater awareness of personal rights of those with mental illness and the development of strategies to manage the spiralling costs of provision of institutional care. Indeed, the first antipsychotic agent chlorpromazine was

only produced by the chemist Paul Charpentier in 1950 with its first use following work by Pierre Deniker and Jean Delay in 1952, where they ascertained that daily injections of chlorpromazine improved both thinking pattern and behaviour in psychotic patients (Turner, 2007). In 1954, chlorpromazine started to be used by psychiatrists to treat psychosis replacing a variety of invasive procedures including electroconvulsive therapy (ECT) and insulin shock therapy (Healy, 2004).

These advances in treatment and increased awareness regarding mental illness enabled the development of community mental health services (Hobbs et al., 2000). In the United Kingdom, deinstitutionalisation was supported by findings from a number of large multi-site research studies which supported community care, where benefits in both symptomatology and patient satisfaction were demonstrated (Leff and Trieman, 2000). Concerns expressed in relation to potential negative effects of deinstitutionalisation including homelessness and incarceration, have largely not been realised (Trieman and Leff, 2002). Cohort studies of long-stay psychiatric patients followed up in the community have shown that patients benefitted from their transfer to the community and that serious issues such as homelessness, imprisonment or suicide were an infrequent occurrence (Winkler et al., 2016). Indeed, it has been argued that the deinstitutionalization of long-stay patients with severe and enduring mental illness is among the most significant developments in mental health policy worldwide in the last 50 years (Petersen et al., 2013).

5.1.3 Development of community psychiatry in an Irish context

Planning for the Future (1984) was the blueprint for deinstitutionalization within the Irish mental health service and led to the eventual closure of the large psychiatric institutions that were prevalent throughout Ireland (Department of Health, 1984). The psychiatric hospital at this time was the focal point of the psychiatric service in most parts of the country. This led to

large numbers of patients residing permanently in these hospitals while community facilities were underfunded and underdeveloped. The report called for a wide range of community services, including the relocation of long-stay care into more appropriate settings within the community.

In 1896, there were 11,000 patients, including intellectually disabled and geriatric patients, in Irish psychiatric hospitals. By 1945, when the Mental Treatment Act 1945 was enacted, this number had risen to 19,500 with a peak in numbers in psychiatric hospitals of 21,000 present in 1958. The Report of the Commission of Inquiry on Mental Illness in 1963 was a major step forward in planning services. The Commission recommended improved hospital-based services and the extension of these services into the community. Interestingly, the report stated that "community care is undoubtedly desirable but its success depends upon the development of a number of specialist facilities within the community". This community care initiative was slow to progress. For example, the 1981 census of psychiatric hospitals recorded that (excluding those patients with intellectual disability) approximately 72% of patients had been in hospital for over a year; 39% were aged over 65; and 52% had a diagnosis of schizophrenia. Following the implementation of The Planning for the Future Document (1984), there has been a 72% decline from 11,906 patients in 1984 to 3,314 in 2007 (Mental Health Commission of Ireland, 2007). Of relevance to this study, Our Lady's Hospital in Ennis had 567 inpatients in 1983, with a reduction of 72% to 157 in 1999. In 2000, the rehabilitation team in Ennis commenced the task of transferring these long-term psychiatric patients of the hospital into the community. The hospital finally closed when this resettlement programme was completed in 2002.

The rehabilitation team based in Ennis Co. Clare consisted of a consultant psychiatrist, a non-consultant hospital doctor in psychiatry, approximately 20 staff psychiatric nurses and a part-time occupational therapist. This team was under-resourced to provide comprehensive rehabilitation to the patients in advance of their community transfer. However, the concepts of

rehabilitation; to enhance interpersonal and social functioning, promote independence and to ameliorate symptom severity (Hamden et al., 2011) were utilised in this process.

The Irish government's mental health strategy in their report "A Vision for Change: Report of the Expert Group on Mental Health Policy" (2006), incorporated a 'recovery perspective' into the proposed development and implementation of modern mental health services in the Republic of Ireland. This strategy Included the development of specialist rehabilitation and recovery mental health teams across the country, with the aim that all patients could reach a level of functioning sufficient to live and enjoy a more independent life in the community. Rehabilitation services enable this by for example promoting and facilitating social inclusion and supporting access to housing, employment and leisure activities in the community, although this can be impeded by insufficient resourcing of these teams (Lavelle, 2012).

5.1.4 Quality of Life in chronic psychiatric conditions

QoL and social functioning are acknowledged as core features requiring assessment in patients who suffer severe and enduring mental illness (Kwon and Choi, 2009). Assessment scales incorporating QoL and social functioning allow investigation beyond clinical syndromes and reflect community adjustment such as self-care, interpersonal skills, and occupation (Lehman, 1996). Chronic schizophrenia often leads to long-term and severe impairments that are slow to change and therefore instruments measuring QoL, and functioning needed to be sensitive to incremental changes (Burns and Patrick, 2007). These assessments need to be very specific as for instance, distinguishing impairments in social functioning from negative symptoms can be difficult given that negative symptoms of schizophrenia result in social withdrawal (Burns and Patrick, 2007). However, some studies have found that negative symptoms were unrelated over time to scores on performance- based measures of functional capacity, indicating that the

relationship between negative symptoms and functional outcome are distinguishable (Brissos et al., 2011).

There have been relatively few studies examining former long-stay psychiatric patients transferred into the community. The Vermont Longitudinal Study (1987) found that approximately 50% of patients with chronic schizophrenia followed up 32 years after their discharge from a psychiatric institution, no longer had any active psychotic symptoms detectable. This was a seminal study as it suggested that patients with schizophrenia may have a better prognosis than what was previously considered (Harding et al., 1987). In 1994, a 20-year retrospective study was conducted of approximately 300 psychiatric patients admitted to an inpatient rehabilitation programme in rural Ireland. The study found that 76% of these patients had subsequently been discharged into the community suggesting that the rehabilitation programme instituted had a positive impact functioning in addition to symptomatology allowing for discharge back in to the community (Farragher et al., 1996).

In an earlier five year publication on this study cohort (McInerney et al., 2010), an initial improvement in social functioning one year following community transfer was demonstrated but this improvement was not sustained after five years. However, there were no improvements in patient's domestic skills, community skills or activity levels. Weekly occupation levels increased after 5 years in the community and their level of interests in activities increased over the first year but not after 5 years in the community. No psychometric instruments to measure social functioning were however included at this time-point. Despite this apparent lack of improvement in social functioning over the 5 year period, patients reported being happier in their new residence and expressed a wish to remain living in the community (McInerney et al., 2010). The recommendation from this study was that there should be smaller high support hostels with dedicated rehabilitation training provided to residents in order to optimise their QoL and social functioning. In addition, training for staff and

a multi-disciplinary team who are specialized in rehabilitation psychiatry was deemed to be a priority.

The Team for the Assessment of Psychiatric Services (TAPS) was established in 1985 in the United Kingdom (UK) to evaluate the policy of replacing psychiatric institutions with community based services. One of the TAPS projects was to follow-up long-stay patients discharged from 2 psychiatric hospitals in the UK. This study followed up a cohort of 670 discharged patients over a 5-year period, with assessments of social outcomes and everyday living skills completed. Patients expressed greater satisfaction with their new residence and the authors suggested that the QoL of patients had improved due to patients living in less restrictive conditions, acquiring more confidants and gaining domestic and community living skills. There was however no change in their clinical condition or social behaviour (Leff and Trieman, 2000). In addition, QoL was not formally assessed. A further study by the same authors noted that even individuals initially deemed unsuitable for community transfer, demonstrated an improvement in social skills and functioning at 1 and 5 year follow-up even though their clinical symptomatology was unaltered (Trieman and Leff, 2002). These studies suggest that transfer to the community is at least associated with increased functioning and patient satisfaction, even for patients with enduring mental illness who have spent very significant periods of time in institutional settings.

Table 5.1 below displays the more recent longitudinal studies involving functional outcomes of long-stay psychiatric patients with respect to their clinical characteristics and functional outcomes.

Table 5.1 Longitudinal studies involving functional outcomes of long-stay psychiatric patients*

Study	Study Details	Functional Outcome
Hobbs et al., (2000)	6 years. N=47, 98%=SCZ	No significant difference in SBS.
Leff and Trieman, (2000)	5 years. N=670, 80%=SCZ.	SBS total score was unchanged. Community skills significantly improved.
Lesage et al., (2000)	7 years. N=96; 65%=SCZ	Sociability improved on LCS. Higher scores found on living skills (ILSS).
Trieman and Leff, (2002)	5 years. N= 72; 86% = SCZ	Improvements on SBS and BELS after 5 years; no improvements at year 1.
Priebe et al., (2002)	2 years. N=128; 78% =SCZ.	Improvement in QoL and met needs.
Mastroeni et al., (2005)	5 years. N=97. IT (74% = SCZ), RT (81% = SCZ)	GAF score improved significantly both in the IT group and in the RT group.
Thornicroft et al., (2005)	2 years. N=73. No Dx.	No differences in SBS or social network.
Grinshpoon et al., (2006)	6 month. N=92. All = SSD.	Significant improvement in self-care, impulse control and social functioning.
Ryu et al., (2006)	2 years. N=78, All = SCZ.	Improved social functioning at follow up.
Chan et al., (2007)	5 years. N=30; all SSD.	No change in WHOQOL but improvement in social activities.
Furlan et al., (2009)	4 years. N= 176, 74% SSD.	Improved ADLs and more social contacts.
McInerney et al., (2010)	5 years. N= 87; SCZ = 72%	Deterioration in BELS (self-care and social activation) but improved SBS.
Petersen et al.,(2013)	5 years. SCZ = 80%	Deterioration on SBS. Improved QoL and gains on ILSS.
Nemoto et al., (2014)	5 years. SCZ = 100%	Improved global but not social function.

*Adapted from Kunitoh, 2013. BELS= Basic Everyday Living Skills Schedule; Dx = Diagnosis. GAF= Global Assessment of Functioning; ILSS= Independent Living Skills Schedule; IT= Integrated Treatment; LCS= Level of Care Survey; RT= Routine Treatment; SBS=Social Behavior Schedule; SCZ= Schizophrenia; SSD = Schizophrenia Spectrum Disorders.

5.1.5 Rehabilitation services

Rehabilitation services can be defined as: “A whole system approach to recovery from mental ill health which maximises an individual`s quality of life and social inclusion by encouraging their skills, promoting independence and autonomy in order to give them hope for the future and which leads to successful community living through appropriate support” (Killaspy et al., 2005).

In the Planning for the Future document (1984), rehabilitation psychiatry was concerned with returning skills to a person impaired by mental illness. It also involved fostering the ability of individuals to cope in domestic, occupational, industrial, social and recreational settings. The wording is slightly different in the A Vision for Change (2006) document where ‘rehabilitation’ is described as a facilitative process that enables disadvantaged individuals to access as independent a life as possible in social, cultural and economic terms. Thus, A Vision for Change (2006) places a greater emphasis on independent living.

The clinical symptoms of schizophrenia include positive, negative and cognitive symptoms that all have deleterious effects on QoL and functional ability (Harvey et al., 2011). The aim of rehabilitation with long-stay psychiatric patients (many of whom have schizophrenia) is to improve psychosocial function and QoL through a variety of therapeutic interventions. The goal of these interventions is to achieve a level of functioning sufficient to live a more independent life in the community (Juckel and Morosini, 2008). A recent study in Ireland found that patients in receipt of eighteen months of rehabilitation displayed superior social functioning compared to those with a similar clinical and socio-demographic profile who received treatment as usual (Lavelle, 2012).

5.2 Aims and hypotheses:

The aim of this study was to investigate the QoL and psychosocial functioning of former long-term psychiatric inpatients 10 years after transfer to the community, and to assess if sociodemographic and clinical predictors at baseline were associated with QoL at follow up. The hypotheses are:

1. Prolonged prior hospitalisation will be associated with lower QoL at follow-up.
2. Higher social functioning at baseline will be associated with higher QoL at follow up.
3. Less social behavioural problems at baseline will be associated with higher QoL at follow up.
4. A diagnosis of schizophrenia will be associated with lower QoL at follow up compared to those without a diagnosis of schizophrenia.
5. Improvements in social behaviours problems during the follow-up period will be associated with higher QoL.

5.3 Methods

5.3.1 Study Design

This is a 10-year longitudinal follow up study of patients who transferred from long-stay psychiatric institutions to residential placements in the community.

5.3.1.1 Participants

At the time of the hospital closure there were 157 patients remaining of the long-stay patients of Our Lady's Hospital in Ennis, Co Clare in Ireland. Patients were invited to participate in the study if they met the inclusion and exclusion criteria. 87 patients were eligible, and all consented to participate in the study in January 2001. All patients were discharged in the first quarter of 2001 and none received intensive rehabilitation prior to discharge. Of these, 35 completed follow-up assessments 10 years later. Death certificates were obtained from those who deceased (n=38) during the course of the study.

5.3.1.2 Inclusion criteria

Patients were included in the study if they:

1. Had been an inpatient for greater than one year in Our Lady's hospital, Ennis.
2. Did not meet any exclusion criterion.

5.3.1.3 Exclusion Criteria

1. History of a learning disability (intelligence quotient < 70)
2. Had a diagnosis of dementia

5.3.1.4 Ethical Approval

The study was approved by the Clinical Research Ethical Committee, Our Lady's Hospital, Ennis, Co. Clare prior to study commencement in 2001 for the baseline assessment. The Clinical Research Ethical Committee of Limerick Regional Hospital, HSE Mid-West approved the 10 year follow-up study as the previous ethics committee at Our Lady's Hospital Ennis was no longer in situ at this time point. Written informed consent was required for all patients participating in the study. An information sheet describing the study was sent to each participant at least 2 weeks prior to contact from the principal investigator (SMI) inviting study participation.

5.4 Assessments

The same assessments were carried out at baseline and follow up after 10 years. The only difference was that the Quality of Life Scale (QLS) was conducted at the follow up time frame only. This scale was added in order to provide a formal QoL scale in addition to the proxy measures of QoL and social functioning used at the baseline period. The QLS measure was used as the main outcome variable for the 10 year follow up study.

5.4.1 Social Behaviour Schedule (SBS)

The SBS was designed specifically to assess the functioning of patients with severe and long-lasting psychiatric disabilities and in particular to identify behaviours that result in dependence on psychiatric care (Wykes and Sturt, 1986). The SBS covers behaviour areas exhibited by patients with enduring mental health difficulties including communication difficulties, social relationships, risk or unacceptable behaviours, hygiene and underactivity. It is a 21-items schedule, with items rated on a 5-point anchored scale (0=no problem or acceptable behaviour, to 4 =serious problem). Therefore the total scale scores range from 0 to 105. The scale is completed from an informant's description of the patient's behaviour over the past month, with a higher score representing lower levels of functioning. Items include; communication skills, socialisation skills and exhibiting inappropriate social behaviours. The SBS scale takes 15 - 20 minutes to complete and includes interviews with both the patient and a member of nursing staff. Reliability studies have provided kappa coefficients ranging from 0.67 to 0.94 (Wykes and Sturt, 1986).

5.4.2 Basic Everyday Living Skills (BELS)

The BELS consists of 26 items, each of which describes a particular behaviour. This schedule was developed to supplement the Social Behaviour Schedule, which did not cover many of the activities that became available to patients in the community. It aims to evaluate changes in the performance of these skills in patients when they move from institutional settings into the community. The scale is completed after interview with the participant and a staff member familiar with the participant. This allows for ratings to be attributed to the performance of the participant on a range of every-day tasks and skills including cooking, shopping and cleaning. There are four outcome measures; self-care, domestic skills, community skills and an activity

and social relations score. Higher scores indicate better skills in a particular area. With respect to the reliability of BELS; 22 of the 26 items have kappa values above 0.7 and 4 are between 0.4 and 0.7 (Leff et al., 1996).

5.4.3 Community Placement Questionnaire (CPQ)

The CPQ is a standardized staff-completed questionnaire designed to assess the needs of long-stay residents who have been in hospital for more than one year and who do not have a diagnosis of dementia. This 37-item questionnaire is completed on the basis of the person's observed performance in the past month on a range of items including social functioning, problem behaviours and need for accommodation. The CPQ provides a social functioning score (SF) which is a composite measure of ten items of the questionnaire covering areas such as self-care, domestic skills, community skills, social skills and social responsibility. Higher scores indicate better social functioning. The scale has been found to be reliable and valid (Clifford et al., 1991).

5.4.4 Patient's Attitude Questionnaire (PAQ)

The PAQ rates the attitudes of patients towards their treatment settings and is framed specifically to assess attitudinal change during transfer of patients from hospital (Thornicroft et al., 1993). This 19-item interviewer administered questionnaire also sought to elicit the patient's views about the care they were receiving and about what in particular they liked or disliked about where they were living. Depending on the individual question there are three to eight options provided on each item. No total score is available. The mean test-retest reliability value was 0.51, and the average inter-rater value was 0.82 (Thornicroft et al., 1993).

5.4.5 Quality of Life Scale (QLS)

The QLS scale (see Section 2.8.2.1) was conducted with all 35 patients who were assessed at ten year follow up. Each semi-structured interview took approximately 45 minutes to complete. It will be used as the outcome variable in the regression analyses to follow.

5.5 Statistical analysis

All analyses were conducted using Statistical Package for the Social Science (SPSS) version 23.0 for windows (IBM SPSS Inc., New York, 2015).

5.5.1 Data analysis

Means and standard deviations (SDs) were attained for all appropriate demographic, QoL and social functioning variables. Baseline and follow-up mean values for selected demographic and psychosocial variables for participants were compared by conducting paired t-tests. Bivariate correlations (Pearson r) were investigated between QLS total score, QoL and social functioning variables at baseline and follow up. Significance level was set at the 0.05 level.

5.5.2 Linear regression

To identify independent baseline predictors of QoL at follow up, linear regression modelling was used, with the R^2 statistic indicating the magnitude of the relationship between the independent and the dependent variable (QLS). The independent variables were age, gender as well as the clinical variables of diagnosis (schizophrenia or not schizophrenia), SF, SBS total score and the four BELS scale variables. For the analysis of change over time; in addition to the baseline variables, change in SF, change in SBS items, change in BELS questionnaire measures over the 3 year follow up period were included in the regression analysis.

To identify independent baseline predictors of deceased status at follow up, logistic regression modelling was used, with the R^2 statistic indicating the magnitude of the relationship between the independent and the dependent variable. The independent variables again consisted of; age, gender, diagnosis and the social functioning measures used in the previous regression analysis. The dependent variable was the whether the patient survived until the follow up period.

Chapter 6

QoL of long-stay patients discharged into the community

Results

6.1 Results

6.1.1 Sociodemographic characteristics of participants

Of the 87 patients who initially enrolled in the study in 2002, 35 participants (40.2%) completed follow-up assessments 10 years later. The 52 (59.8%) other participants comprised 38 (43.7%) participants who died within the follow-up period and 14 (16.1%) participants who did not complete follow-up assessments. Of the 14 non-completers, 7 were excluded due to the development of dementia, 5 were un-contactable (4 residing in independent accommodation and 1 had emigrated), 1 was in prison and 1 refused to participate. There were no baseline statistically significant differences on any demographic or clinical variables between completers, non-completers and participants who died (Table 6.1). No significant differences in baseline SF, SBS or BELS subscales scores were demonstrated between completers and non-completers.

The QLS mean score of study completers at follow up was 81.5 (SD =25.2) with a range of 38-119. Community placements are detailed in Table 6.1 with 32 (91.4%) participants initially moving to high support hostel settings.

On the PAQ, 27 (77.1%) of the 35 patients followed up reported that they preferred living in the community compared to the hospital setting, 7 (20.0%) did not have a preference, and one individual (2.9%) stated they would have preferred remaining in the institution. When participants were asked where in the community they would ideally like to currently reside, 21 individuals (60.0%) expressed a preference to remain in their current residence and 14 (40%) expressed a preference to live elsewhere. These 14 patients lived in high support hostels. Their preferences were either to return to live with others in a shared home (17%), to live with family (11%), to live independently (9%). One patient was undecided (3%) where else they wanted to live. These responders who preferred to live elsewhere were all living in a high support

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I am confused by this – do you mean return to their institutional setting, or move to a less supported hostel such as a group home ?

A high supported hostel is a shared accommodation

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environment with less privacy and autonomy than may have been the case in other living arrangements. While this more restrictive environment could have had an impact of their QLS scores, this was not the case as there was no difference in QLS scores between those who whose to live in their current residence or who expressed a preference to live elsewhere.

Of the 38 participants who died within the follow-up period, 34 (90%) were male and the mean baseline age was 69.7 (SD = 9.7) years of age (Table 6.1). Thirty-five patients died due to "natural causes" and included deaths secondary to circulatory disorders (n=19), respiratory disorders (n=7), neoplasms (n=6) and gastrointestinal disorders (n=3). Those who died during the study were predominantly older, male, with a diagnosis of schizophrenia (see table 6.1 for description).

Three male patients died due to "unnatural causes", two of whom died by drowning and one by asphyxiation. There were no unnatural deaths among women during this time. Nineteen of the 38 participants (50%) who died, did so within 4 years of hospital discharge. The demographics of the baseline cohort and those who attended follow up are outlined below in Table 6.1.

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Preferences included living in a less supported group home establishment (n = x, %), to reside with other family members (n = x, x%) or to live independently (n = x, x%).
All of these potential residences would be associated with a greater level of autonomy compared to their current living situation. Individuals expressing this preference demonstrated no statistical differences in relation to QLS scores compared to those stating a preference to continue to reside in their present residence. This suggests that expressing a wish to live in a less restrictive environment did not confound QoL data.

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Table 6.1 Demographics and clinical characteristics of baseline and follow-up cohorts

	Baseline (n=87) n (%) Range={}	**Study Completers (n=35)** N (%) Range={}	**Study Non-Completers (n=14)**	**Participants who died (n=38)** N (%) Range={}
Age at baseline	64.6 (11.9) {25-93}	62.4 (10.3) {41-88}	55.7 (15.0) {25-78}	69.7 (9.7) {46-93}
Male gender	74 (85)	28 (80)	13 (93)	34 (90)
Length of inpatient stay (yrs.)	12.1(14.1) {1-54}	12.2 (14.3) {1-42}	8.4 (9.9) {1-30}	12.7 (14.9) {X-Y}
Diagnosis of schizophrenia	63 (72)	26 (74)	11 (79)	26 (68)
Community Placement:				
High Support Hostel	32 (91.4)	22(62.9)		27 (71.0)
MSH	3 (8.6)	6 (17.1)		7 (18.4)
Nursing Home	0 (0.0)	6 (17.1)		3 (7.9)
Independent Residence	0 (0.0)	1 (2.9)		1 (2.6)
CPQ:				
Social Functioning (SF)	2.3 (0.7) {1.2-3.6}	3.1 (0.6) {1.8-3.9}*	2.1 (0.7) {1.0-3.2}	1.9 (0.7) {1.0-3.8}
SBS- Total score	21.9 (9.4) {2-52}	21.4 (10.5) {3-47} *	21.6 (12.5) {2-52}	22.3 (7.4) {11-46}
BELS Questionnaire:				
Self-Care	24.8 (6.5)	28.8 (8.9)	24.5 (9.6)	23.9 (6.4)
Domestic Skills	7.8 (5.4)	12.6 (8.6) *	10.0 (7.6)	6.3 (4.3)
Community Skills	4.6 (2.3)	7.6 (4.3) *	5.4 (3.0)	4.4 (1.9)
Activities/Social Relations	8.7 (4.8)	13.8 (5.2) *	8.5 (5.0)	7.9 (5.0)

Paired t-tests; *p < 0.05 Baseline vs study completers. Data are Mean (SD).
Abbreviations: BELS = Basic Everyday Living Skills questionnaire; CPQ = Community Placement Questionnaire; MSH= Medium Support Hostel; SBS = Social Behaviour Scale; yrs. = years.

6.2 Completer data compared to baseline

At 10 year follow up, there were statistically significant improvements noted in functional measures compared to baseline assessment. Statistically significant improvements in

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community skills, activity and social relations and domestic skills were demonstrated over the 10 year period (Table 6.1). Despite changes in self-care not being statistically significant, there was a trend towards improvement ($p < 0.08$). Compared to baseline, increased SF was noted at follow up ($t = -6.4$, $p < 0.0001$). This finding suggests that on average patients adapted well to their new environment despite their increasing age and possible greater degree of physical impairment. Similarly, there was a statistically significant improvement on the SBS ($t = 8.4$, $p < 0.001$), suggesting a reduction in socially unacceptable behaviours at follow up, although individual items on the scale were not examined in this study.

6.3 Baseline predictors of deceased patients over the course of the study

A logistic regression was conducted where the dependent variable was if the patient was deceased or not at follow-up with the independent variables including baseline variables of age, gender, length of stay, diagnosis (schizophrenia or not schizophrenia), SF score, total SBS score, and the QoL variables (domestic skills, self-care, community skills and activity/social relations). This regression analysis explained 18% of the variance ($R^2 = 0.18$, SEE = 0.48, $F = 1.7$, $p < 0.09$. Only older baseline age was predictive of being deceased in this analysis (Table 6.2).

Table 6.2 Baseline predictors of deceased status

	B (SE)	t	p
Age	0.005 (0.31)	**2.74**	**0.008**
Gender	0.03 (0.17)	0.17	0.86
LOS (years)	0.004 (-0.007)	-0.06	0.96
Diagnosis*	0.02 (0.015)	0.13	0.89
Social Functioning (SF)	-0.10 (0.12)	-0.88	0.38
Total SBS baseline	0.01 (0.01)	0.02	0.98
SC- baseline	-0.01 (0.01)	-0.19	0.85
DS- baseline	-0.02 (0.01)	-1.25	0.22
CS- baseline	0.07 (0.01)	1.62	0.11
AS- baseline	-0.01 (0.01)	-0.05	0.96

Abbreviations: AS= Activities and Social Relations; CS= Community Skills; DS=Domestic Skills; LOS= Length of Stay; QLS, Quality of Life Scale; SBS=Social Behaviour Scale; SC=Self-Care.
*Divided into schizophrenia or not schizophrenia

6.4 Baseline predictors of QLS at follow up

A linear regression analysis was conducted where the dependent variable was QLS (completed at follow up). Independent variables were SF score, total SBS score, the BELS scores for self-care, domestic skills, community skills and activity/social relations age, gender and diagnosis (schizophrenia/non-schizophrenia). The model represented 41% of the variance ($R^2 = 0.41$, SEE = 23.6. $F = 1.57$, $p < 0.18$). In this analysis, total SBS score at baseline predicted QoL at 10 year follow up ($p < 0.02$) (see Table 6.3).

Table 6.3 Baseline predictors of QLS at follow up

Independent Variables	**B (SE)**	**t**	**p**
Age	-0.25 (0.48)	-0.52	0.61
Gender	6.11 (11.31)	0.54	0.59
LOS (years)	-0.02 (0.38)	-0.05	0.96
Diagnosis*	7.37 (9.79)	0.75	0.46
SF Baseline	10.42 (8.78)	1.19	0.25
Total SBS Baseline	-1.63 (0.63)	-2.60	**0.02**
SC- baseline	-0.27 (1.5)	-0.18	0.86
DS- baseline	0.33 (1.16)	0.28	0.78
CS- baseline	-2.92 (3.91)	-0.75	0.46
AS- baseline	-1.15 (1.69)	-0.68	0.50

*Divided into schizophrenia or not schizophrenia; Abbreviations: AS = Activities and Social Relations; CS = Community Skills; DS = Domestic Skills; LOS = Length of Stay; QLS = Quality of Life Scale; SBS = Social Behaviour Scale; SC=Self Care.

6.5 Baseline and change predictors of QLS at follow up

A linear regression analysis was conducted with QLS as the dependent variable (which was completed at follow up). The independent variables were the baseline and changes in SF score, baseline and changes in total SBS score, and baseline and changes in the BELS measures of self-care, domestic skills, community skills and activity/social relations as well as age, gender and diagnosis (schizophrenia/non-schizophrenia). The model (see Table 6.4) explained 79% of the

variance (R^2 = 0.79, SEE = 11.2. F = 8.56, $p < 0.001$). In this analysis, lower SBS at baseline ($p < 0.02$), predicted higher QOL at 10 year follow up.

Table 6.4 Baseline and change predictors of QLS at follow up

Independent Variables	**B (SE)**	**t**	**p**
Age	-0.25 (0.25)	0.97	0.35
Gender	-2.19 (6.7)	-3.28	0.75
Length of stay (years)	0.27 (0.21)	1.34	0.20
Diagnosis*	0.41 (5.28)	0.77	0.94
SF baseline	-8.99 (10.9)	-0.82	0.43
SF change	6.63 (9.11)	0.73	0.48
Total SBS baseline	-2.1 (0.77)	-2.72	**0.02**
Total SBS change	1.39 (0.70)	1.99	0.06
SC- baseline	-1.01 (1.12)	-0.89	0.39
SC- change	-0.01 (0.53)	-0.07	0.96
DS baseline	1.22 (0.84)	1.45	0.17
DS change	-1.23 (0.68)	-1.80	0.09
CS baseline	-0.62 (2.15)	-0.29	0.78
CS change	0.33 (1.04)	0.13	0.90
AS baseline	2.34 (1.31)	1.78	0.09
AS change	-1.26 (0.66)	-1.71	0.10

*Divided into schizophrenia or not schizophrenia; Abbreviations: AS= Activities and Social Relations; CS= Community Skills; DS=Domestic Skills; LOS= Length of Stay; QLS, Quality of Life Scale; SBS=Social Behaviour Scale; SC=Self-Care; SF=social functioning.

Chapter 7

Discussion

7.1 Summary of main findings

In the cohort of patients who completed 10-year follow-up assessments, significant improvements were noted in several functional measures. Indeed, the only functional measure that did not demonstrate a significant change compared to baseline (self-care on the BELS questionnaire) demonstrated a non-significant improvement. Of particular importance, social behaviour and social functioning scores improved significantly over the ten year period, suggesting that community placement had a positive impact on the participant's ability to integrate into their new community environment. It is likely that such functional improvements found in the study completers are generalisable to the entire study cohort, as there were no significant difference in baseline scores for any of the functional measures between those who completed the study and those who were unable to participate at follow-up.

7.2 Cohort morbidity/mortality over the course of the study

The mortality rate in this cohort was 44% (n=38), with half of these dying within 4 years of being transferred out of the long-stay psychiatric hospital. Petersen et al (2013) found that approximately 11% (21) of their sample of 189 patients had died during a 5 years of follow-up period, although they had a younger sample (mean age 47 years, range 22-80) and 50% had spent less than 3 years in the institution.

There was substantial physical health morbidity experienced by this cohort that may have contributed to this high mortality rate. Unfortunately, we do not have accurate data in relation to the smoking status of this cohort; however it is known that approximately 75% of individuals with enduring mental health difficulties residing in mental health facilities smoke cigarettes on a daily basis (Lohr and Flynn, 1992; Feeney and Hallahan, 2011). Many of the study participants

who died had conditions potentially related to cigarette smoking (respiratory and cardiac related deaths).

The 3 unnatural male deaths in this study included two deaths by drowning and one by asphyxiation all of which were probable suicides, albeit not recorded as such in the coroner's verdict despite strong suggestion from the death certificates. A previous Irish study similarly examining individuals discharged from a psychiatric institution noted a slightly lower rate of probable suicide (4/298 - 1.3%), however, unnatural deaths were not recorded and thus the rate of probable suicide in the 20 year follow-up period may have been under-reported (Farragher et al., 1996).

A number of international studies have noted similar findings to our study. Lesage and colleagues (1990) in their 7 year follow-up study of patients discharged from residential institutions noted a 3.3% suicide rate (2/61 individuals) and Brown and colleagues (2010) in their 13 year study noting a 4% rate of unnatural deaths (15/370 individuals). Thus, it is likely that our findings are consistent with the literature in relation to the rate of probable suicides in a cohort of individuals discharged from long-stay psychiatric institutions. Indeed, our rates over a 10-year period are consistent with those noted in populations of individuals with enduring mental health difficulties that have not previously resided in long-stay psychiatric institutions (Das-Munshi et al., 2016).

7. 3 Comparison of functioning at 10-year follow-up relative to baseline

This study incorporated multiple measure of social functioning; the SBS, BELS and CPQ were used to represent this cohort of patients as accurately as possible from a functional perspective. The improvements made in social functioning over the follow up period is a positive finding as it implies that patients adapted well to their new environment despite their increasing age and likely higher degree of physical impairment. The findings are particularly

positive given that little formal rehabilitation was provided to patients prior to community transfer. By comparison, Mastroeni et al. (2005) found that social functioning improved in a former long-stay cohort that received intensive rehabilitation (workshops included those on interpersonal communication and social skills, enhancing personal self-care, structured problem solving and other cognitive behavioural strategies) relative to a treatment as usual (TAU) group (Mastroeni et al., 2005). A Japanese longitudinal study of 78 patients with chronic schizophrenia who received psychosocial skills training prior to discharge, found improved global and social functioning after 2 years in the community and that pre-discharge length of stay as well as age of onset of psychiatric illness, predicted this outcome (Ryu et al., 2006).

There was a statistically significant improvement in this current long-stay cohort on all the BELS functional measures over the ten year period except for the self-care subscale on this questionnaire, although this result showed a trend towards significance. A multi-site UK study found that while community skills improved significantly over a 5 year period in a large cohort transferred from an institution, it was domestic skills that did not maintain the improvements made in the first year post-discharge (Leff and Trieman, 2000). An earlier 5 year follow up study of the cohort in this thesis, found deterioration in domestic skills and levels of social activation, likely reflecting both the fact that meals were provided for patients in their residence and that they were an aging cohort with physical comorbidities (McInerney et al., 2010).

There was a statistically significant reduction on the total SBS score over the course of the study, and therefore an improvement in socially unacceptable behaviours at follow up. Hobbs and colleagues found no change in the social behaviour (using total SBS score) in a cohort of 40 long-stay patients discharged into the community following a 2 year follow up period , although there was symptomatic improvement and greater life satisfaction reported (Hobbs et al., 2000). Other studies have similarly reported either no change (Leff and Trieman, 2000; Thornicroft et al., 2005) or deterioration in social behaviour (Petersen et al., 2013). In the Canadian patients experienced an increase in both mild and severe behavioural problems (as assessed on the SBS) from baseline to follow up after 5 years but despite this, reported improved independent living skills and overall life satisfaction (Petersen et al., 2013). It may be the case that a further follow

up in later years will lead to improvement in social behaviour as occurred in the this 10 year study relative to its earlier 5 year result. There does not appear to be any particular pattern of clinical characteristics that readily explains the variation in social behavioral change after community transfer with respect to social behavioural problems, as those that improve are not necessarily younger or had less years of hospitalisation. It is likely that social functioning and behaviour are only minimally associated with the level of symptomatology in patients with enduring mental health difficulties given the low correlations ($r < 0.3$) noted in a number of studies between these constructs in similar cohorts of patients (Heinssen et al., 2000; Bellack et al., 2004; Ryu et al., 2006; Cella et al., 2014).

The study findings provide evidence for the clinical effectiveness of community placement and for former long-stay patients to facilitate improvement in their social functioning. The accumulation of living skills could be related to the practicalities of living in the community with some residents moving to less restrictive settings. Indeed there were twice as many patients in medium support hostels at follow up (n=6) than at time of transfer to the community (n=3), though 6 patients required the higher level of care needed in a nursing home at follow up. One patient who previously had spent 24 months in a locked ward who had a very high total SBS score (reflecting inappropriate behaviours) was living in independent accommodation at the end of the study, had significantly improved social functioning and his QLS scores were in the highest quartile for this cohort.

Despite the level of disability and complexity present in this cohort of participants and the limited therapeutic interventions available (e.g. access to a full-time occupational therapist), a significant improvement across many behavioural and functional assessments were demonstrated.

7.4 Baseline predictors of QLS at 10-year follow-up

Most studies of former long-stay psychiatric patients transferred to the community have either had pre-post transfer design or have been compared to a matched sample that remained in the hospital setting. In this study, as in that by Ryu and colleagues discussed earlier, regression analysis was used to investigate what baseline variables may be associated with QLS at follow up. Lower levels of socially unacceptable behaviours at baseline (as measured by the SBS) were predictive of higher QLS score at follow up and there was a statistical trend towards an improvement in the total SBS score over time to also be associated with higher QLS scores. This suggests that despite varied levels of active rehabilitation over the 10 year period for this cohort, those who had less problem social behaviours were better able to adapt and benefit from the transfer to community living. Based on this finding, challenging social behaviours represent a potential target for rehabilitation services in order to maximise patient QoL and functioning in the community, although, given the observational nature of the current study, further research is required to clarify whether specific interventions to reduce challenging social behaviours will actually result in improved quality of life.

7.5 Strengths and limitations of the study

This study has a number of key strengths. These include the very long follow up period and uniqueness, being one of the first longitudinal studies in Ireland to evaluate functional measures and quality of life in individuals transferred to the community after periods of long-stay in psychiatric institutions.

The study is longitudinal in design and had a high follow-up rate (73%) in those that were not deceased. In the 14 participants that were not followed-up, data was present regarding their

baseline functioning and about their current living situation. Indeed, given that 5 of the 7 individuals who did not have dementia that were uncontactable were residing independently, it is probable that our results under-estimate the improvement in functioning at 10-year follow-up. This study included comprehensive and multi-faceted validated assessments of functioning, with the CPQ specifically designed to measure functioning in previous long-stay residents of psychiatric hospitals. The results of this study are strengthened by attaining reliable data from experienced nursing staff who were all very familiar with the patients.

This study also had a number of limitations. There was no control sample of matched hospitalised patients as is the case in other longitudinal studies and the data collection was also unblinded as the same rater of QLS (SMcI) was involved in the assessment of social functioning. There was limited clinical data pertaining to smoking status, and clinical management over the course of the study including hospital admissions and pharmacological and psychotherapeutic management. The collection of such data would have added to the value of interpreting the results. For example, social behavioural improvement may have been due to changes in antipsychotic medication usage. While there was a limited number of patients followed up due to the mortality over the course of the study and loss to follow up, it must also be noted that the baseline scores on functioning were similar in this group to those that completed the study and thus it is highly probable that the results relating to QoL and improved functioning are generalisable.

7.6 Future Work

Future work could also aim to replicate these findings in patients moving from long-term rehabilitation units or high-support hostels to independent residences. Attaining predictive factors for functioning and QoL for this cohort of patients might enable mental health professionals provide more targeted supports post-discharge to enable optimal functioning and

QoL. This study indicates that patients moving from long-stay psychiatric institutions can have long term positive outcomes and improved functioning, even if they have chronic and enduring mental illness and have had long durations of stay. Even in the absence of extensive and fully resourced rehabilitation team supports, significant improvements in a range of social and behavioural function were identified. The ongoing development of rehabilitation services and greater provision of opportunities for independent or less supported living are also tentatively supported by this study and will form the basis of ongoing research on this patient cohort.

The functional gains demonstrated in the present study may have allowed patients to move to an even less restrictive environment such as from a high support hostel to a medium support hostel. Despite such progression, 73% remained in high support accommodation. This likely reflects a lack of investment in less supported housing and rehabilitation teams to facilitate transfer to such accommodation. Given appropriate resources and supports greater independence for this and similar cohorts is possible. Indeed one could argue that "institutionalisation" in the community is perpetuated by not supporting individuals to reside in the lowest support accommodation possible for them, even if this is associated with a certain degree of risk that such a move would not be successful (Ryan et al., 2004; Lavelle, 2012).

The Vision for Change (2006) mental health strategy recommended the development of comprehensive specialist rehabilitation and community recovery services but there has sadly been a lack of clarity on pathways of care, and there remains inadequate resources and infrastructure to achieve the aims of social inclusion and recovery for those with longer term and complex mental health problems outlined in the strategy (Taylor et al., 2009).

7.7 Conclusion

The findings from this study suggest that community living for former long-stay patients facilitates improvement in their social functioning and quality of life, even after lengthy periods of stay in a psychiatric institution. Lower social behaviour problems at baseline predicted QLS at follow up and therefore, social behaviour may be marker of more benign illness or better resilience in those patients. While the process of deinstitutionalisation is largely complete, the SBS could be used as a marker of poor clinical stability in community samples of chronic patients.

Despite the absence of dedicated rehabilitation services, these patients were able to enhance their domestic, community and activation skills for ten years after they left an institutionalized environment. This has important implications in relation to reducing the mental/physical health and social burden for service users with severe and enduring mental health problems, their families and for society in general.

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This needs additional expansion and care
"social behaviour may be a marker of more benign illness" – is not clear
Less difficulties in xxx suggest xxx

I would expand here stating how this measure may be useful for people transferring between different grades of hostel accommodation , moving to other services (Simon housing), etc – Particularly as easy to undertake
Repeatable over time …

Chapter 8

Thesis Summary

This thesis set out to explore predictors of quality of life in two different cohorts with psychotic illness. The first was an FEP cohort where there was a mix of an affective and non-affective psychosis groups. In linear regression analysis, higher negative symptoms at baseline assessment were predictive of lower QoL at follow-up as was a greater reduction in negative symptoms over time. Diagnosis (affective/non-affective psychosis), age, gender or positive symptoms demonstrated no significant predictive value.

In addition to the clinical information we collected, we also had a reduced number of patients who underwent repeat neuroimaging. Left LV volume enlargement over the 3 year period predicted lower QoL at follow up. This finding of LV enlargement is one of the most replicated neuroimaging findings in psychosis. Uniquely, in this study, LV enlargement was directly associated with QoL.

The former long-stay patients living in the community had relatively high quality of life on the QLS scale despite their many years in the psychiatric institution with a psychotic illness. A lower level of social behavioural problems at baseline was associated with a higher QLS score. This translates those whom had fewer problems in areas such as communication and inappropriate social behaviours at the time of community transfer who were those had higher rated quality of life 10 years later.

Both acute and chronic studies show that there can be good clinical and socio-behavioural outcomes despite a psychotic illness. The findings from this thesis favours assessment of QoL and social functioning early in the course of psychotic illness so that areas of remediation can be identified at an early stage such as negative symptoms or socio-behavioural problems can be targeted given their negative impact on the QoL on those with psychosis.

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APPENDIX 1

QUALITY OF LIFE SCALE (QLS)

This instrument is designed to evaluate the current functioning of non-hospitalized schizophrenic persons apart from the presence or absence of florid psychotic symptomatology or need for hospitalization. It assesses the richness of their personal experience, the quality of their interpersonal relations, and their productivity in occupational roles.

It is intended to be administered as a semi-structured interview. Each item consists of three parts. First, a brief statement is provided to help the interviewer understand and focus on the parameter to be assessed. Second, a number of suggested questions are provided that may help the interviewer begin his exploration with the subject. Finally, a seven-point scale is provided for each item, with a brief description at four points to help the interviewer make his judgment and unlabeled points.

The questions provided are just suggestions. They are to be altered or supplemented as needed. Each item should be explored as much as required to allow the rater to make a good clinical judgment. The intent of the schedule is to assess limitations due to psychopathology or personality deficits. Adjustments should be made by the rater when extraneous factors are clearly and unambiguously involved (e.g., decreased social contact due to serious physical illness).

All items should be rated. Circle the appropriate number on each item scale.

SCORING: Mean scores of the following subsca1es and total (prorate items 1 and 12 for missing data as indicated in the manual).

Subscale Scores:

I. Interpersonal Relations (1-8): _____

II. Instrumental Role (9-12): _____

III. Intrapsychic Foundations (13-17, 20, 21): _____

IV. Common Objects and Activities (18, 19):___

III plus IV (13 thru 20): _____

Total Score (Items 1-21): _____

1. RATE INTIMATE RELATIONSHIPS WITH HOUSEHOLD MEMBERS

This item is to rate close relationships with significant mutual caring and sharing with immediate family or members of the subject's current household.

0	1	2-	3	4	5	6	9
Virtually no Intimacy		Only sparse and intermittent intimate interactions		Some consistent intimate interactions but reduced in extent or intensity; or intimacy only present erratically		Adequate involvement in intimate relations with household members or immediate family	Score Here if lives alone; no immediate family nearby

Suggested questions:

Are you especially close with any of the people you currently live with or your immediate family?

Can you discuss personal matters with them?

How much have you talked with them?

What are these relationships like?

Can they discuss personal matters with you?

What sorts of things have you done together?

When at home, have you spent much time around your family or were you generally alone?

Note: (For Factor and Total Scores, prorate this item on the basis of Items 2 through 8.)

2. RATE INTIMATE RELATIONSHIPS

This item is to rate close relationships with significant mutual caring and sharing, with people other than immediate family or household members. Exclude relationships with mental health workers.

0	1	2-	3	4	5	6
Virtually absent		Only sparse intermittent relations		Some consistent intimate relations but reduced in number or intensity; or intimacy only present erratically		Adequate involvement with intimate relationships with more than one other

Suggested questions:

Do you have friends with whom you are especially close other than your immediate family or the people you live with?

Can you discuss personal matters with them?

How many friends do you have?

How often have you spoken with them recently, in person or by phone?

What have these relationships been like?

Can they discuss personal matters with you?

3. RATE ACTIVE ACQUIANTANCES

This item is to rate relationships with people based on liking one another and sharing common activities or interests but without the intimate emotional investment of the above item. Exclude relationships with mental health workers and other household members.

0	1	2-	3	4	5	6
Virtually absent		Few active acquaintances		Some ongoing active acquaintance but reduced contact and limited shared activity		Adequate involvement with active acquaintances

Suggested questions:

Apart from close personal friends, are there people you know with whom you have enjoyed doing things?

Have you been with people as a part of clubs or organize activities? How many?

How often have you gotten together with them?

What things have you done together?

Have you had extra social contact with co-workers, such as going to lunch together or going out after work?

4. RATE LEVEL OF SOCIAL ACTIVITY

This item is to rate involvement in activities with other people done for enjoyment.

Exclude social activity that is primarily instrumental for other goals, for example, work and school. Exclude psychotherapy.

0	1	2-	3	4	5	6
Virtually absent		Occasional social activity but lack of regular pattern of such activity, or limited only to activity with immediate family or members of household		Some regular social activity but reduced in frequency or diversity		Adequate level of regular social activity

<u>Suggested questions:</u>

How often have you done things for enjoyment that involve other people?

What sort of things?

Have you participated in clubs or other organized social groups?

5. RATE INVOLVED SOCIAL NETWORK

This item is to rate the extent to which other people concern themselves with the person, care about his fortunes or know about his activities. Exclude mental health workers.

0	1	2-	3	4	5	6
Virtually absent		Minimal in number or degree of involvement, and/or limited to immediate family		Presence of some involved social network but reduced in number of degree of involvement		Adequate involved social network in both extent and in degree of involvement

Suggested questions:

Are there people who have been concerned about your happiness and well-being?

How many?

How did they show it?

If some important and exciting thing happened to you, who would you contact or inform?

Are there people who often provided you emotional support or help in day-to-day matters such as food, transportation, and practical advice?

Are there people you could turn to or depend on for help if anything happened?

6. RATE SOCIAL INITIATIVES

This item is to rate the degree to which the person is active in directing his social interactions - what, how much, and with whom.

0	1	2-	3	4	5	6
Social activity almost completely dependent on initiatives of others		Occasional social initiative, but social life significantly impoverished due to his pattern of social passivity, or initiative limited to immediate family		Evidence of some reduction of social initiative, but with only minimal adverse consequences on his social activity		Adequate social initiative

Suggested questions:

Have you often asked people to do something with you, or have you usually waited for others to ask you?

When you have had an idea for a good time, have you sometimes missed out because it's hard to ask others to participate?

Have you contacted people by phone?

Have you tended to seek people out?

Have you usually done things alone or with other people?

7. RATE SOCIAL WITHDRAWAL

This item is to rate the degree to which the person actively avoids social interaction due to his discomfort or disinterest.

0	1	2-	3	4	5	6
Active avoidance of virtually all social contact		Tolerates that social contact required for meeting other needs, but very little social contact for its own sake, or lack of withdrawal only with immediate family		Some satisfying and enjoyable social engagement, but reduced due to avoidance		No evidence of significant social withdrawal

<u>Suggested questions:</u>

Have you felt uncomfortable with people?

Have you turned down offers to do things with other people? Would you if you were asked?

Have you done this even when you have had nothing to do?

Have you avoided answering the phone?

How has this interfered with your life?

Have you dealt with people only when it's necessary to accomplish something you want?

Have you stayed to yourself at home?

Have you preferred to be alone?

8. RATE SOCIOSEXUAL RELATIONS

This item is to rate the capacity for mature intimate relations with members of the opposite sex and satisfying sexual activity. The wording assumes a heterosexual preference. In clear cases of consistent homosexual preference, reword accordingly and rate these same capacities.

0	1	2-	3	4	5	6
No interest in opposite sex, or active avoidance		Some limited contact with opposite sex but superficial with avoidance of intimacy; or sexual activity as just physical release without emotional involvement; or relationships marked by severe and chronic disruption, dissatisfaction or affective chaos		Relationships with some intimacy and emotional investment, predominantly satisfying, and perhaps some sexual expression or physical signs of affection		Usually has satisfying relationships, emotionally rich and intimate and appropriate sexual expression and physical signs of expression

<u>Suggested questions if single:</u>

Have your social activities involved women (men)?

Have you avoided them or found it too uncomfortable to deal with them?

Have you dated?

Did you have one or more girlfriends? (boyfriends?)

Have the relationships been satisfying?

Have emotionally involved were you?

Were you in love?

Were you having sexual activity?

Was it satisfying?

Did you show physical signs of affection, such as hugging and kissing?

Suggested questions if married or living with someone:

Were you happy in your relationship with your partner?

Have you done many things together?

Did you talk together much?

Did you discuss personal thoughts and feelings?

Did you fight much?

Has your sex life been satisfying?

Did you show physical signs of affection such as hugging and kissing?

Did you feel close to her (him)?

9. RATE OF EXTENT OF OCCUPATIONAL ROLE FUNCTIONING

This item is to rate the amount of role functioning the person is attempting, not how well nor how completely he is succeeding. For homemakers, consider whether for a person with normal efficiency the responsibilities would represent a full-time job seeking activity.

0	1	2-	3	4	5	6
Virtually no role functioning		Less than half-time		Half-time or more, but less than full-time		Full-time or more

Suggested Questions:

Have you had a job?

How many hours a week did you work?

Suggested Questions for students:

Were you involved in school in addition to work?

What sort of education program were you pursuing?

How many classes were you taking?

How much time did school take per week?

Were you also working, caring for children or responsible for housekeeping?

Suggested questions for homemakers:

How much was involved in taking care of your home and family?

Were you raising children?

What were your responsibilities in the home?

How much did other people help with these responsibilities?

10. RATE LEVEL OF ACCOMPLISHMENT

This item is to rate the level of success and achievement in fulfilling the particular role the person has chosen to attempt.

0	1	2-	3	4	5	6
Attempting no role function or performing at level so poor as to imminently threaten the ability to continue in that role		Functioning just well enough to keep position with very low level of accomplishment		Generally adequate functioning		Very good functioning with evidence of new or progressive accomplishments and/or very good functioning in some areas

Question the subject regarding salary and raises, the challenge and responsibility of the job, praise or reprimands from employer, adequacy of interaction with co-workers, absenteeism, promotions or demotions.

For students, question regarding grades, the difficulty of the curriculum, praise or criticism from teachers, adequacy of interaction with other classmates, class attendance, completion of assigned work, and extracurricular activities.

For homemakers, question regarding the adequate performance of required tasks such as cooking, shopping, washing dishes, cleaning, dusting, laundry, management of household budget, physical care of children, and meeting the emotional needs of children.

Question further regarding praise or criticism by family members about either housekeeping or child raising.

11. RATE DEGREE OF UNDEREMPLOYMENT

This item is to rate the degree to which the existing extent of and accomplishment in occupational role functioning reflects full utilization of the potentiality and opportunities available to the person. Consider innate abilities, physical handicaps, education, economic and social culture factors. Obviously, limitations directly reflecting any mental illness or personality disorder should not be considered in estimating the person's potential.

0	1	2-	3	4	5	6
Almost complete failure to actualize potentials		Significant underemployment of abilities or unemployed but looking for work actively.		Somewhat below the person's capacity		Role functioning commensurate with person's abilities and opportunities

Suggested questions:

This item requires a complex judgment.

Ask any further questions needed to clarify the abilities and opportunities of this individual.

12. RATE SATISFACTION WITH OCCUPATIONAL ROLE FUNCTIONING

This item is to rate the extent to which the person is comfortable with his choice of role, the performance of it, and the situation in which he performs it. It also is to rate the extent to which it provides a sense of satisfaction, pleasure, and fulfillment to him.

0	1	2	3	4	5	6	9
Pervasive unhappiness and dissatisfaction with occupational role		Little or no definite evidence of unhappiness or dissatisfaction, but role does not provide any positive pleasure or fulfillment. Perhaps boredom is evident.		Little or no discontent and some limited pleasure in work		Rather consistent sense of fulfillment and satisfaction, perhaps in spite of some limited complaints	Not applicable if patient not involved in any occupational role functioning

Suggested questions:

Did you like your work or schooling?

Would you have preferred to be doing something else?

Do you plan a change? Why?

Did you get good feelings from doing your work – pleasure, fulfillment, etc.

Did your work or school make you feel good about yourself?

Are you enthusiastic about your job?

Do you look forward to going to work?

Note: (This item should be rated 2 if item #9 is rated less than 3. For Factor and Total scores, prorate this item on the basis if items 9 through 11.)

13. RATE SENSE OF PURPOSE

This item is to rate the degree to which the person posits realistic, integrated goals for his life. If the person's current life reflects such goals, it is not necessary that he (she) be planning a change in order to be judged to have a good sense of purpose.

0	1	2	3	4	5	6
No plans, or plans are bizarre, delusional, or grossly unrealistic		Has plans, but they are vague, somewhat unrealistic, poorly integrated with one another, or of little consequence to the person's life		Realistic and concise plans for next year or so but little integration into long-range life plan		Realistic, concise, and integrated plans, both short- and long-range

Suggested questions:

What makes life worth living for you?

Do you think much about the future?

Have you set any goals for yourself?

What do you anticipate your living and working situation to be a few months from now?

What plans do you have for your life over the next year or so – personal as well as job related ones?

14. RATE DEGREE OF MOTIVATION

This item is to rate the extent to which the person is unable to initiate or sustain goal-directed activity due to inadequate drive.

0	1	2	3	4	5	6
Lack of motivation significantly interferes with basic routine		Able to meet basic maintenance demands of life, but lack of motivation significantly impairs any progress or new accomplishments		Able to meet routine demands of life and some new accomplishments, but lack of motivation results in significant underachievement in some areas		No evidence of significant lack of motivation

Suggested questions:

How have you been going about accomplishing your goals?

What other things have you worked on or accomplished recently?

Have there been tasks in any area that you wanted to do but didn't because you somehow didn't get around to it?

Has this experience of just not getting around to it interfered with your regular daily activities?

How motivated have you been?

Have you had much enthusiasm, energy, and drive?

Have you tended to get into a rut?

Have you tended to put things off?

15. RATE CURIOSITY

This item is to rate the degree to which the person is interested in his surroundings and questions those things he doesn't understand. Exclude interest in hallucinations or delusions or other psychotic products. However, pathological preoccupation with psychotic products or other themes may limit curiosity or interest in other things.

0	1	2	3	4	5	6
Very little curiosity or interest in new topics or events		Some sporadic curiosity, but not pursued in thought or action		Some curiosity and time spent thinking about topics or interest and some actual effort to learn more about them		Curiosity about a number of topics and some effort to learn more about some of them such as reading, asking questions and planned observation

Suggested questions:

How often have you seen or heard about something that you wanted to know more about or understand better?

What sorts of things?

Have you done anything to learn more about them? Please specify.

Have you read the newspapers, or listened to the news on TV or radio?

Were you interested in any issues in current events or sports?

How curious about things have you been?

16. RATE ANHEDONIA

This item is to rate the person's capacity to experience pleasure and humor. Do not rate anhedonia that presents as the result of a clear and observable depressive syndrome, e.g., agitation, crying, marked feelings of wickedness and worthlessness, etc. However, anhedonia accompanied by apathy and withdrawal from which depression may be inferred should be rated. Ask any questions necessary to determine the presence of depression and its effect on hedonic capacity. This is to be distinguished from the capacity to display affect, which is not rated here.

0	1	2	3	4	5	6
Nearly complete inability to experience pleasure or humor		Some sporadic and limited experiences of pleasure or humor but a predominant lacking of these capacities		Some regular experiences of pleasure & humor but reduced in extent & intensity		No evidence of anhedonia or can be explained completely by concurrent depression or anxiety

<u>Suggested questions:</u>

Have you been able to enjoy yourself?

How often have you really enjoyed or gotten satisfaction from something you were doing?

How often did you choose to do something that struck you as amusing or made you feel like laughing?

Did you have trouble getting enjoyment from things that seemed like they should be fun?

Do other people seem to get more enjoyment in things than you do?

Did you often spend the better part of the day bored or disinterested in things?

17. RATE TIME UTILIZATION

This item is to rate the amount of time passed in aimless inactivity -sleeping during the day, lying in bed, sitting around doing nothing or in front of the TV or radio when not particularly interested.

0	1	2	3	4	5	6
Spends the vast majority of his day in aimless activity		Spends about half of his days in aimless activity		Some excessive aimless inactivity but less than half his day		No excessive aimless inactivity beyond the normal amount required for relaxation

Suggested questions:

Did you spend much time doing nothing just sitting around or in bed?

Did you spend much time watching TV or listening to music - were you really interested or just had nothing better to do?

Did you sleep much during the day?

How much of your days were spent in these ways?

How have you utilized your time?

Did you tend to waste time?

18. RATE COMMONPLACE OBJECTS

This item assumes that basic participation in living in this culture nearly always requires a person to possess certain objects.

0	1	2	3	4	5	6
Absence of nearly all commonplace objects (0 items)		Major deficit of commonplace objects (3-4 items)		Moderate deficit (7-8 items)		Little or no deficit (11-12 items)

Suggested questions:

For this question, inquire about each of the 12 items listed below.

Are you wearing or carrying the following?

(1) a wallet or purse

(2) keys

(3) a driver's license

(4) a watch

(5) a credit card

(6) a Social Security or Medical Assistance card

Do you have with you at your place of residence the following?

(1) a map of the city or area

(2) your own alarm clock

(3) a comb or hair brush

(4) an overnight bag

(5) a library card

(6) postage stamps

19. RATE COMMONPLACE ACTIVITIES

This item assumes that basic participation in living in this culture nearly always requires a person to engage in certain activities.

0	1	2	3	4	5	6
Absence of nearly all activities (0 items)		Major deficit (3-4 items)		Moderate deficit (7-8 items)		Little or no deficit

Suggested questions:

For this item inquire about each of the 8 items listed below.

Which of the following have you done in the past two weeks?

(1) read a newspaper

(2) paid a bill

(3) wrote a letter

(4) gone to a movie or play

(5) driven a car or ridden public transportation alone

(6) shopped for food

(7) shopped for other than food

(8) eaten in a restaurant

(9) taken a book or record out of the library

(10) participated in a public gathering

(11) attended a sporting event

(12) visited a public park or other recreational facility.

20. RATE CAPACITY FOR EMPATHY

This item is to rate the person's capacity to regard and appreciate the other person's situation as different from his own - to appreciate different perspectives, affective states and points of view. It is reflected in the person's description of interactions with other people and how he views such interactions. Specific probing to elicit the person's description and assessment of relevant situations can be done at this time if sufficient data has not emerged thus far in the interview.

0	1	2	3	4	5	6
Shows no capacity to consider the views and feelings of others		Shows little capacity to consider the views and feelings of others		He can consider other people's views and feelings but tends to be caught up in his own world.		He spontaneously considers the other person's situation in most instances, can intuit the other person's affective responses, and uses this knowledge to adjust his own responses.

Suggested questions:

Consider someone you are close to or spend a lot of time with.

What about them irritates or annoys you?

What about you irritates or annoys them?

What things do they like?

What things that you do please them?

If they appear upset, how do you usually react?

If you have an argument or difference of opinion with them, how do you handle it?

Are you usually sensitive to the feelings of others?

Are you affected very much by how other people feel?

21. RATE CAPACITY FOR ENGAGEMENT AND EMOTIONAL INTERACTION WITH INTERVIEWER

This item is to rate the person's ability to engage the interviewer, to make him feel affectively in touch and acknowledge him as a participant individual in the encounter, and to react in a give and take way.

This is a global judgment based on the entire interview.

0	1	2	3	4	5	6
Interviewer feels virtually ignored with essentially no sense of engagement, with very little reactivity		Very limited engagement		Engagement somewhat limited or present erratically		Consistently good engagement and reactivity