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REVIEW PAPER

The Psychological Impact of Predictive Genetic Testing for Huntington's Disease: A Systematic Review of the Literature

S Crozier · N Robertson · M Dale

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Abstract Huntington's disease (HD) is a neurodegenerative genetic condition for which a predictive genetic test by mutation analysis has been available since 1993. However, whilst revealing the future presence of the disease, testing may have an adverse psychological impact given that the disease is progressive, incurable and ultimately fatal. This review seeks to systematically explore the psychological impact of genetic testing for individuals undergoing pre-symptomatic mutation analysis. Three databases (Medline, PsycInfo and Scopus) were interrogated for studies utilising standardised measures to assess psychological impact following predictive genetic testing for HD. From 100 papers initially identified, eight articles were eligible for inclusion. Psychological impact of predictive genetic testing was not found to be associated with test result. No detrimental effect of predictive genetic testing on non-carriers was found, although the process was not found to be psychologically neutral. Fluctuation in levels of distress was found over time for carriers and non-carriers alike. Methodological weaknesses of published literature were identified, notably the needs of individuals not requesting genetic testing, as well as inadequate support for individuals registering elevated distress and declining post-test follow-up. Further assessment of these vulnerable individuals is warranted to establish the extent and type of future psychological support.

Keywords Genetic testing · Predictive testing · Huntington's disease · Psychological impact · Systematic review

S. Crozier · N. Robertson (✉)
Department of Clinical Psychology, University of Leicester,
104 Regent Road, Leicester, UK
e-mail: nr6@le.ac.uk

M. Dale
Adult Mental Health Psychology, Leicestershire Partnership
NHS Trust, Leicester, UK

Introduction

Huntington's disease (HD) is an autosomal dominantly inherited neurodegenerative condition with a worldwide prevalence rate of between 0.4 and 5.7 people per 100,000 (Pringsheim et al. 2012). The average age of onset for the disease is 40 years with a typical disease trajectory of 10–20 years until death (Myers, 2004). HD is characterised by a triad of impairments in movement, cognition and affect. Currently the disease is incurable although treatments may improve quality of life.

Although HD was first thoroughly described in 1872 (Huntington, 1872), it was only in the 1980s that genetic markers for HD were located within chromosome four (Gusella et al. 1983). Through a process of tracing inheritance markers across generations of affected and unaffected family members, the first genetic testing by linkage analysis was developed and offered to those at risk in 1986. Initially, linkage analysis was only considered for research purposes but was later used in clinical settings offering at-risk individuals testing within 95 % accuracy of likely future development of HD (Huntington's Disease Society of America, 2001).

Linkage analysis was replaced in 1993 by direct mutation analysis following the isolation of the gene responsible for HD (Huntington's Disease Collaborative Research Group, 1993). HD was definitively found to result from an expansion of the trinucleotide repeat (CAG) coding for a protein involved in nerve cell function. Essentially, whilst healthy individuals will have between 11 and 26 repeats of the CAG trinucleotide, those who go on to develop HD have a CAG repeat length of 40 and above. Mutation analysis testing allowed assessment for the presence of the mutation gene, giving individuals 100 % certainty of their status as a carrier of the condition (Evers-Kiebooms & Decruyenaere, 1998). Rare outcomes of testing are results that fall within the reduced penetrance range (36–39 CAG repeats), whereby individuals may or may not develop

symptoms of the disease; or those with intermediate alleles (27–35 CAG repeats) who will not develop symptoms of the disease themselves, but their children will be at-risk of HD. There is difficulty establishing frequency of these rare outcomes due to a limited number of presentations (Myers, 2004).

Following the identification of the specific gene in 1993, international collaborators have developed guidelines for predictive genetic testing and recommendations regarding the provision of genetic counselling (International Huntington Association and World Federation of Neurology Research Group on Huntington′s International Huntington Association and the World Federation of Neurology Research Group on Huntington′s Chorea 1994; MacLeod et al. 2012).

Prior to the availability of a specific genetic test, between 56 % and 81 % of individuals at-risk of HD expressed a desire for testing (Koller & Davenport, 1984; Tyler & Harper, 1983), however after testing was offered, figures suggested a maximum of 20 % uptake (Craufurd et al. 1989; Quaid & Morris, 1993). This discrepancy may be explained by the complexity inherent in decision making to undergo predictive genetic testing. Diverse motives may operate such as reducing uncertainty, shaping reproductive choices, responding to reactions of family members and practical planning, as well as fears of coping in the event of a positive test result (Decruyenaere et al. 1997).

As well as shaping any decision to proceed with testing, psychological issues are prominent, in reactions to an unfavourable genetic test, after which intense distress and potential for suicidal risk has been documented (Kessler, 1987; Kessler et al. 1987). Such reactions may be understandable given the potential for definitive genetic certainty of developing the disease, as well as response to absence of effective treatments and inevitable decline (Gooding et al. 2006). For these reasons, in conditions such as HD with little hope of ameliorating interventions, the ethical and psychological implications of predictive genetic testing is of paramount importance. Such understanding permits sensitivity to those who may be psychologically at-risk and consideration of possible interventions (Salkovskis & Rimes, 1997).

Knowledge of genetic status has been revealed to have both a positive and negative impact on an individual′s life (Duncan et al. 2008). Circumscribed qualitative research exploring the experiences of individuals who have undergone predictive genetic testing for HD has revealed diverse responses. Amongst these are regret and distress associated with anticipated life change and limitations, and a loss of hope, as well as increased appreciation of life and relief from uncertainty (Hagberg et al. 2011). Adverse psychological impact has been suggested, irrespective of test result, in carriers through adjustment processes to inevitable progression to diagnosis, or for non-carriers, an adaptation to survivor guilt (Hayden & Bombard, 2005). This latter term encompasses the burden of remaining healthy whilst others will test positive and develop the disease. Psychological difficulties in the aftermath of testing have also been attributed to over-optimism regarding the impact of favourable test results in as many as 10 % of individuals identified as non-carriers (Huggins et al. 1992).

Various psychological models have endeavoured to encapsulate reactions to predictive genetic testing. Notable amongst these is the Common Sense Model of self-regulation of health and illness, (Leventhal et al. 1998). This model advances the idea of parallel processes of appraisal and coping, using both cognitive and emotional strategies, as a means of reducing distress caused by a threat to health (Leventhal et al. 2001). Using illness representations (the cognitions implicit in appraisal), threat of a disease is appraised with respect to its cause, controllability and consequence over time, with health behaviours argued as the means by which threat is managed. Concurrent to this process, the model suggests emotional processes trigger alternative, usually unconscious, coping strategies to manage fear and uncertainty. Within this approach, HD can be constructed as uncontrollable in its development and fatal in consequence, making it likely to be appraised as highly threatening and therefore highly distressing. A distressing period of "knowing about not knowing," can lead an at-risk individual to seek out predictive genetic testing (Konran, 2003) and this process of applying for testing can therefore be seen as a coping strategy for managing at-risk status by providing control to the individuals through seeking certainty and knowledge (Gooding et al. 2006).

An equally useful perspective on the threat to those who are genetically at-risk is offered by Rolland and Williams (2005). In their family systems model they argue that appraisals of health threat encompass a three way interaction of disease-specific typology, time phase and functioning. Disease-specific typology is based on an individual′s appraisal of disease likelihood, clinical severity, timing of onset and availability of treatments. For those at risk of HD, with its 50 % inheritance pattern, clinical impact in middle-adulthood, lack of treatment options and subsequent fatality, their disease appraisals are likely to be more intensely negative than for other genetic conditions. The identification of a genetically at-risk population from predictive genetic testing has prompted the definition of disease within the model to be broadened to include the time prior to clinical diagnosis. In addition to the disease time phases highlighted in the family systems illness model (Rolland, 1984), non-symptomatic disease time phases of awareness, pretesting crisis, test/post-testing crisis and long term adaption have also been identified. The psychological impact of disease may therefore resonate throughout these time phases; beyond predictive genetic testing but before clinical diagnosis.

From both these models, an individual′s representation of a disease, and its meaning, may influence coping strategies and functioning and has framed exploration of psychological reactions of individuals undergoing predictive genetic testing. To date, findings have been equivocal. A systematic review,

undertaken over a decade ago examining global psychological consequences of predictive genetic testing (of which HD respondents were non-separate) identified no abnormally high or increased levels of distress in individuals assessed up to three years post-test, however a sub-group of individuals were identified as having high levels of anxiety or depression post-testing (Broadstock et al. 2000). By contrast, a narrative review of psychological consequences from HD-specific predictive genetic testing highlighted differential psychological impact between individuals found to be carriers and those found to be non-carriers in the short-term (Meiser & Dunn, 2000). These differences may reflect the differing review methodologies and included studies. More recently the adverse psychological impact of predictive genetic testing has been suggested irrespective of test result, although psychological distress appears to be manifest along differing time trajectories (Almqvist et al. 2003).

Aims of the Current Review

Theory, and a circumscribed evidence base suggests that there may be differential psychological impact of predictive genetic testing dependent on disease type. This finding, allied with research revealing significantly higher levels of distress in individuals undergoing predictive genetic testing for HD in comparison to other genetic conditions (Dudok DeWit et al. 1998; 1997), prompted the authors' initial focus on the specific psychological impact of predictive genetic testing in individuals at-risk of HD.

Whilst the impact of predictive genetic testing in HD specifically has been explored in two non-systematic reviews (Meiser & Dunn, 2000; Hayden & Bombard, 2005), both are limited by a focus on predictive genetic testing conducted by the discontinued linkage analysis, albeit alongside mutation analysis. A singular focus on the psychological impact of testing via mutation analysis is warranted given some evidence of elevated depression, pre- and post-test (Adam et al. 1995; Codori et al. 1997). Explanatory theories may also imply that those receiving predictive results through mutation analysis may experience more adverse reactions given the definitive nature of the result.

Reviews to date have also reflected a lack of published empirical research, particularly examining comparisons between individuals choosing to undergo predictive testing and those who do not, and an absence of studies addressing cognitive or behavioural consequences of predictive testing (Broadstock et al. 2000). Additional limitations are evident because of the circumscribed periods of post-test follow-up that were undertaken because of the relatively recent adoption of mutation analysis at the time they were undertaken. Since it is now a decade since mutation analysis was introduced, the current review was felt timely to examine longer-term follow-up data, to enrich evaluation of the psychological impact of predictive genetic testing.

The aim of the current review was therefore to review systematically the published evidence base exploring the psychological impact of the process of pre-symptomatic predictive mutation analysis testing for HD in individuals at-risk of the disease. Examination of impacts is hoped to guide development and delivery of clinically supportive services and shape future research focus.

Method

Search Strategy

A thorough examination of the available literature was completed with adherence to a systematic search process. An initial scoping search developed a focus with the formation of search strings. This permitted the identification of literature addressing the main aims of the current review. Search strings were grouped to address main focus areas including: psychological impact (psycholog*; impact; effect; consequence), genetic testing (genetic; predictive; testing; screening) and HD (HD; Huntington*).

Searches, conducted in November 2013, and repeated in March 2014, used Medline, PsycInfo and Scopus databases to ensure a range of medical and psychological literature was included. Reference lists from identified papers were examined to identify further relevant literature as well as consultation with researchers in the HD field. To validate the results of the search strings, references were compared with those included within previously published narrative reviews (Meiser & Dunn, 2000; Hayden & Bombard, 2005).

Articles published prior to 1993 were excluded, consistent with the time at which the mutation analysis test was introduced. Searches were limited to peer-reviewed articles in English language.

From the three databases, a total of 157 articles were identified, 80 from Scopus, 26 from PsycInfo and 51 from Medline. A further three articles were identified from consultation with known researchers in the field. With duplicates removed a total of 100 abstracts remained. Titles and abstracts were screened against the eligibility criteria with 33 warranting full text appraisals.

Eligibility Criteria

The full texts of articles were coded for eligibility by the principal researcher with articles excluded if they were:

- Qualitative – requirement of a standardised outcome measure of psychological impact from genetic testing

- Reviews, meta-analyses or narrative accounts of knowledge

Other exclusion criteria included:

- Using a non HD at-risk sample or an HD at-risk sample that was not separable from other genetically inherited conditions
- Using a child sample
- Using confirmatory genetic, prenatal genetic or linkage analysis testing
- Case studies or conference abstracts

Quality Appraisal and Data Extraction

Full articles were independently appraised with regards to conformity to Strengthening the Reporting of Observational studies in Epidemiology (STROBE) combined checklist (Von Elm et al. 2008). Checklists were used to guide researcher's judgements rather than provide quality scores (Da Costa et al. 2011) to ensure quality assessment and evaluation of bias looking at key areas of reporting including description of sample, measures used and statistical analysis performed. Data extraction forms were independently used to code all articles for inclusion. Half the articles to be included were randomly selected and independently coded by the second author for purposes of reliability and validity. Little discrepancy was evident and was clarified through discussion to achieve consensus.

Eligible Papers

A total of eight articles were included within the current review. Reasons for article exclusion were: use of alternative genetic testing methods other than predictive mutation analysis testing (10); no use of standardised measures of the psychological impact of genetic testing (five); and analysis with differing genetic testing procedures or genetically inherited conditions not permitting assessment of data pertaining solely to HD (10). A summary of the article selection process is given in Fig. 1. Only one study had been included in previously published reviews (Decruyenaere et al. 1996).

Results

Study Characteristics

Main characteristics of studies included in this review are shown in Table I. Studies were conducted across six countries: Belgium (Decruyenaere et al. 1996); France (Gargiulo et al. 2009); USA (Horowitz et al. 2001); Sweden (Larsson et al. 2006; Wahlin et al. 2000); Germany (Lickleder et al. 2008); and the Netherlands (Timman et al. 2004; Witjes-Ané et al. 2002). Recruitment of participants in all papers was via a single centre genetic clinic associated with a university hospital, with the exception of one study in which recruitment was through contacts with multiple professionals working in the field and response to an advert placed in a HD-specific newsletter (Lickleder et al. 2008).

One study employed a retrospective design (Gargiulo et al. 2009) and a further study used a between-subjects design (Lickleder et al. 2008). All other studies used a prospective, repeated measures design with baseline measures compared with as few as two and as many as five follow-up points. Study sample sizes ranged from 34 (Wahlin et al. 2000) to 134 (Witjes-Ané et al. 2002) with a mean age ranging from 36.9 (Wahlin et al. 2000) to 41.9 years (Gargiulo et al. 2009). The percentage of female participants within the studies ranged from 50 % (Wahlin et al. 2000) to 68 % (Horowitz et al. 2001).

Constructs used to assess psychological impact to genetic testing included; depression and hopelessness (seven studies), anxiety (two studies), distress (three studies), psychological well-being (five studies) and self-injurious/suicide tendency (two studies). Depression and hopelessness were measured using the Beck Depression Inventory (BDI: Beck et al. 1961) or Beck Hopelessness Scale (BHS: Beck, 1974). Anxiety was measured by the State Trait Anxiety Inventory (STAI: Spielberger, 1983) with measures of general and specific, state and trait anxiety. Distress was measured with the Impact of Events Scale (IES: Horowitz et al. 1979) giving cognitive and affective indices associated with intrusion and avoidance. Psychological well-being was determined through use of Baron's Ego Strength Scale from the Minnesota Multiphasic Personality Inventory (MMPI: Graham, 1987), General Health Questionnaire-30 (GHQ-30: Goldberg & Williams, 1988), Global Severity Index (GSI) of the Brief Symptom Inventory (BSI: Derogatis & Melisaratos, 1983) or the Short Form Health Questionnaire (SF-12: Bullinger & Kirchberger, 1998). The Self Injurious Behaviour Scale (SIBS: Fox et al. 1989) was used to measure self-injurious or suicide tendency. The Unified Huntington's Disease Rating Scale (UHDRS: Huntington Study Group, 1996) was used in one study as measure of affect and behaviour change looking at depression, low self-esteem, anxiety, suicidal thoughts, obsessions, compulsions, irritable behaviour, disruptive or aggressive behaviour, delusions and hallucinations.

Psychological Impact of HD GeneticTest Result

Eight studies were identified which compared the psychological impact of HD genetic testing contingent on test result as summarised in Table II. Three studies with a follow-up of up to ten years post-test have highlighted no significant difference between individuals given a carrier status and those

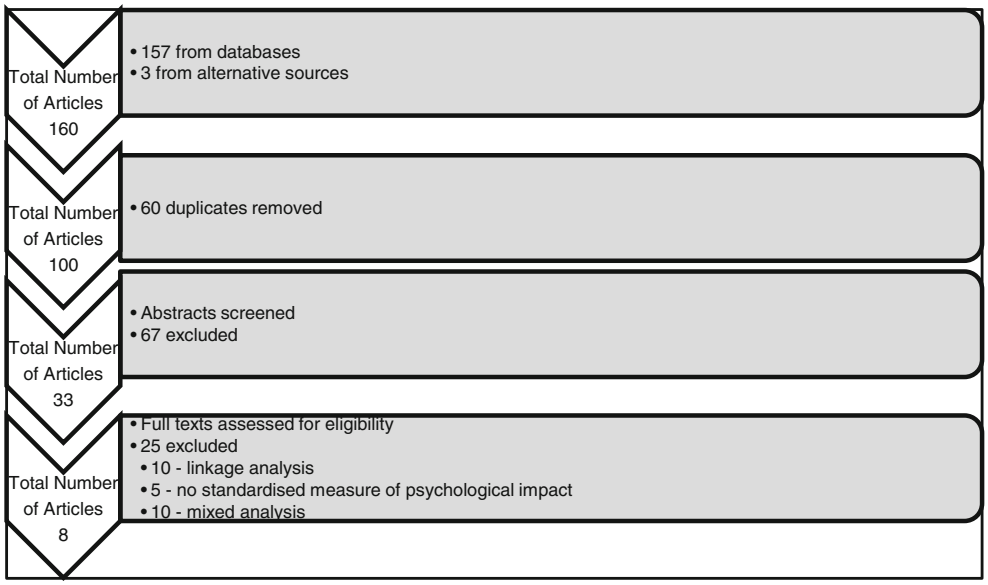

Fig. 1 PRISMA flowchart (Moher et al. 2009) depicting number of articles excluded at each stage of eligibility screening

given a non-carrier status (Decruyenaere et al. 1996; Timman et al. 2004; Wahlin et al. 2000).

No study suggested a detrimental psychological effect of genetic testing for HD when the test outcome was favourable (revealing non-carrier status) compared to when test outcome was undesirable (revealing carrier status). Some studies reported a positive psychological impact in non-carriers, with a significantly lower level of hopelessness and distress (Gargiulo et al. 2009), depression and low self-esteem, alongside non-significant trends for aggression and compulsive behaviours up to nine years post-test (Witjes-Ané et al. 2002). However, neither study accounted for pre-test levels of these constructs. Where baseline levels were taken into account, only one study revealed a significantly lower level of deperssion in non-carriers compared to carriers two years post-test (Larsson et al. 2006). No significant differences in levels of suicidal thoughts or behaviour were seen between carriers and non-carriers (Wahlin et al. 2000). Whilst one paper reported levels of self-injurious behaviours and suicidal thoughts of insufficient magnitude to complete analysis (Larsson et al. 2006), another reported elevated levels for both carriers and non-carriers (Wahlin et al. 2000).

Table I Characteristics of studies assessing psychological impact of genetic testing in HD

Author (Country)	Number of Participants			Assessment Time Points	Measures Used
	Non-Carrier	Asymptomatic Carrier	Symptomatic Carrier		
Decruyenaere et al. 1996 (Belgium)	31	22		Baseline, 1 m, 1 yr	BDI STAI MMPI (Baron′s) MMPI (Baron′s)
Gargiulo et al. 2009 (France)	62	57		3 m – 9 yr	BDI BHS STAI IES
Horowitz et al. 2001 (USA)	44	15	17	Baseline, 3 m, 6 m, 12 m	IES BDI
Larsson et al. 2006 (Sweden)	35	58		Baseline, 2 m, 6 m, 12 m, 24 m	SIBS GHQ-30 BDI
Lickleder et al. 2008 (Germany)	52	54	15	Baseline	BDI GSI SF-12
Timman et al. 2004 (Netherlands)		61		Baseline, disclosure, 6 m, 18 m, 3 yr, 7-10 yr	BHS IES GHQ-30
Wahlin et al. 2000 (Sweden)	21	13		Baseline, 2 m, 6 m,12 m, 24 m	GHQ-30 BDI SIBS
Witjes-Ané et al. 2002 (Netherlands)	88	46		Baseline (0–61 m), 18 m	UHDRS

wk: weeks; m: months; yr: years

BDI: Beck Depression Inventory; STAI: State Trait Anxiety Inventory; MMPI: Minnesota Multiphasic Personality Inventory;

BHS: Beck Hopelessness Scale; IES: Impact of Events Scale; SIBS: Self Injurious Behaviour Scale;

GHQ-30: General Health Questionnaire-30; GSI: Global Severity Index; SF-12: Short Form-12;

UHDRS: Unified Huntington′s Disease Rating Scale

Table II Studies exploring differences in psychological impact of genetic testing for HD between carriers and non-carriers

Author	Length of Follow Up	Construct Measured	Findings			Power for Moderate Effect Size 0.5 for 2 groups or 0.25 for 3 groups (%)
			Non-Carrier	(Asymptomatic) Carrier	Symptomatic Carrier	
Decruyenaere et al. 1996	1 yr	BDI	NS	NS		38
		STAI	NS	NS		
		MMPI	NS	NS		
Gargiulo et al. 2009	3 m – 9 yr	BDI	Sig less frequent	Sig more frequent		68
		BHS	Sig lower	Sig higher		
		STAI	NS	NS		
		IES	Sig lower	Sig higher		
Horowitz et al. 2001	1 yr	IES	Sig lower	NS	Sig higher	33
		BDI	NS	NS	NS	
Larsson et al. 2006	2 yr	BDI	Sig lower	Sig higher		57
Lickleder et al. 2008	Baseline	BDI	Lower[a]	Lower[a]	Higher[a]	68
		GSI	Lower[a]	Lower[a]	Higher[a]	
		SF-12	Higher[a]	Higher[a]	Lower[a]	
Timman et al. 2004	7 yr – 10 yr	BHS	NS	NS		44
		IES - Intru	NS	NS		
		- Avoid	NS	NS		
Wahlin et al. 2000	2 yr	GHQ-30	NS	NS		28
		BDI	NS	NS		
		SIBS	NS	NS		
Witjes-Ané et al. 2002	18 m	UHDRS - depr	Sig lower	Sig higher		68
		- estm	Sig lower	Sig higher		
		- aggr	Lower	Higher		
		- comp	Lower	Higher		

[a] Statistical comparisons not completed and therefore cannot be determined whether statistically significant difference

m: month; yr: year: NS: not significant; Sig: significance to the level $p<0.05$

BDI: Beck Depression Scale; STAI: State Trait Anxiety Inventory; MMPI: Minnesota Multiphasic Personality Inventory: BHS: Beck Hopelessness Scale:

IES: Impact of Events Scale; GSI: Global Severity Index: SF-12: Short Form-12; GHQ-30: General Health Questionnaire-30;

SIBS: Self Injurious Behaviour Scale; UHDRS: Unified Huntington's Disease Rating Scale;

intru: intrusion; avoid: avoidance; depr: depression; estm: low self-esteem; aggr; aggressive behaviour; com: compulsions

Six of the eight studies comparing the psychological impact of predictive genetic testing on carriers and non-carriers, excluded symptomatic carriers at follow-up in an attempt to obtain a homogenous group free from bias. Understandably this undermines representative sampling and reduces generalizability of findings. Horowitz *et al.* (2001) compared non-carriers with both asymptomatic and symptomatic carriers finding a significant difference in the levels of distress one year post-test. Symptomatic carriers reported significantly higher levels of distress than non-carriers but no significant difference between asymptomatic carriers and non-carriers was evident, which may suggest psychological difficulties are associated with disease manifestation.

Three studies revealed no clinically significant levels for either carrier or non-carrier groups on measures of psychological impact (Larsson et al. 2006; Lickleder et al. 2008; Wahlin et al. 2000). Clinically significant levels of depression were only evident for symptomatic carrier groups (Lickleder et al. 2008), or when a lower cut-off was used for the BDI (Gargiulo et al. 2009).

Psychological Impact of HD Genetic Testing Over Time

The differential courses of psychological impact associated with genetic test results was explored in three studies (Decruyenaere et al. 1996; Timman et al. 2004; Witjes-Ané et al. 2002) presented in Table III. No study reported a significant change in the extent of depression, anxiety, low self-esteem or scored ego strength on standardised tests for carriers over time. After an initial peak in hopelessness after the test, carriers′ scores showed a general decrease from one year onwards. Immediately following testing, scores highlighted an increase in distress with an escalation in thoughts and feelings associated with intrusion and avoidance. Symptoms generally declined from one month post-test, although there appeared to be a peak between one and three years post-test,

with avoidance being reported to a higher degree. Scores in aggressive behaviours and obsessions were seen to increase in carriers, irrespective of motor symptoms.

Non-carriers appeared to experience a decrease in depression and anxiety one year post-test and in hopelessness up to ten years post-test, compared to baseline scores. Aggressive behaviours and irritability were seen to improve with increasing time from the test result. The pattern of distress from baseline, repeatedly measured up to ten years post-test, matched the fluctuating course described for carriers.

Non-Specific Predictors of Psychological Impact of HD Genetic Testing

Seven studies explored a range of predictors of psychological impact of testing for HD. Numerous psychological factors were highlighted, including; a prior history of symptoms in the self or family (Decruyenaere et al. 1996; Gargiulo et al. 2009; Larsson et al. 2006; Witjes-Ané et al. 2002), expectation of test result and the result itself (Gargiulo et al. 2009; Horowitz et al. 2001; Lickleder et al. 2008).

Non-specific predictors of psychological impact of HD genetic testing were identified via regression analysis (Decruyenaere et al. 1996; Larsson et al. 2006), factor analysis (Gargiulo et al. 2009) or correlation coefficients (Witjes-Ané et al. 2002). All methods are limited in their ability to infer causation and incompleteness in fully explaining the psychological impact of predictive genetic testing.

Methodological Issues

All the studies within this review acknowledged potential sampling bias, through examining self-selecting participants who actively sought predictive genetic testing, via HD centres who screen out those sought psychologically less ready for testing. No studies in the current review established a difference in the psychological status of individuals at-risk of HD but who declined to undergo genetic testing. A single study discussed three sibling pairs across carrier and non-carrier groups within the sample (Wahlin et al. 2000) which may have created bias in potential survivor guilt in the non-carrier sibling.

Drop-out rates across studies varied markedly, ranging from 5 % over two years (Larsson et al. 2006) to 69 % over 10 years (Timman et al. 2004). Of the eight papers, only Timman et al. (2004) undertook analysis of attrition rates, reporting individuals found to be carriers who subsequently withdrew from follow-up had significantly higher hopelessness, intrusion and avoidance scores and significantly lower psychological well-being scores than carriers who completed follow-ups, perhaps suggestive of an unrepresentative sample.

Only one study utilised a HD-specific measure with the use of the UHDRS (Witjes-Ané et al. 2002). All other measures used were standardised generic measures of psychological constructs found in the general population. Measures appeared to be used in a pragmatic manner to assess impact, rather than explicitly deriving measures from a theoretical understanding of how genetic testing might have effect.

Since HD is a relatively uncommon disease, study sample sizes tended to be small despite reasonably large sampling frames. Consequently many reported a lack of external validity and power in finding an effect (Decruyenaere et al. 1996; Horowitz et al. 2001; Larsson et al. 2006; Lickleder et al. 2008; Wahlin et al. 2000). Post hoc power calculations revealed that indeed, the majority of studies were underpowered. Five studies offered individuals tested by linkage analysis repeat testing with mutation analysis prior to their participation (Decruyenaere et al. 1996; Larsson et al. 2006; Timman et al. 2004; Wahlin et al. 2000; Witjes-Ané et al. 2002). Although not acknowledged by the authors, this may have created bias by increasing psychological burden through being genetically tested twice.

Discussion

This systematic review revealed eight articles that have conducted a focused examination of the psychological impact of pre-symptomatic predictive genetic testing for HD using mutation analysis. No significant differences were seen with regard to psychological impact determined by test outcome. No immediate or detrimental effects were found for individuals identified as non-carriers, rather there was some evidence of a positive psychological impact compared to carriers, albeit not reaching statistical significance. Only once symptomatic carriers were isolated from asymptomatic carriers for analysis, was a significant difference in levels of distress found in comparison to non-carriers (Lickleder et al. 2008). This may be suggestive of distress being a potential early manifestation of the disease.

The course of psychological impact following testing was investigated with evidence of no significant change over time for carriers, with the exception of an initial increase in levels of hopelessness. Behavioural changes were identified with an increase in aggression and obsessions, independent of the presence of motor symptoms, which is supportive of previous research suggesting that mood and behavioural difficulties precede neurological symptoms (Folstein, 1989). Levels of depression, anxiety and hopelessness were seen to decrease in non-carriers as well as a reduction in aggressive behaviour and irritability.

Distress (intrusion and avoidance) was seen to have a fluctuating course over time for both carriers and non-carriers, albeit at a higher level for carriers. This could be as a result of nearing the age of onset of HD for carriers (Timman et al. 2004) with theory suggesting increased distress arising from fatalism (Senior et al. 1999). Survivor guilt, regret of life choices, adaptation to result, denial of result and living within

Table III Studies exploring changes in psychological measures following genetictesting for HD in carriers and non-carriers

Author	Constructs Measured	Test Result	Findings				Power for Moderate Effect Size of 0.5 (%)
			Baseline – 1 m	6 m–1 yr	1 yr – 3 yr	3 yr – 10 yr	
Decruyenaere et al. 1996	BDI	Carrier	No change	No change			61
	STAI		No change	No change			
	MMPi		No change	No change			
	BDI	Non-Carrier	Decreased	Decreased			65
	STAI		Decreased	Decreased			
	MMPI		No change	No change			
Timman et al. 2004	BHS	Carrier	Increased	Return to Baseline	Decreased	Return to Baseline	65
	IES - Intru		Increased	Decreased	Return to Baseline	Decreased	
	- Avoid		Increased	Decreased	Increased	Decreased	
	BHS	Non-Carrier	Decreased	Return to Baseline	Return to Baseline	Return to Baseline	78
	IES - Intru		Increased	Decreased	Return to Baseline	Decreased	
	- Avoid		Increased	Decreased	Increased	Decreased	
Witjes-Ané et al. 2002	UHDRS - depr	Carrier			No change		82
	- estm				No change		
	- aggr				Increase		
	- obs				Increase		
	UHDRS - depr	Non-Carrier			No change		99
	- estm				No change		
	- aggr				Decreased		
	- irrit				Decreased		

m: month; yr: year

BDI: Beck Depression Inventory; STAI: State Trait Anxiety Inventory; MMPI: Minnesota Multiphasic Personality Inventory; BHS: Beck Hopelessness Scale;

IES: Impact of Events Scale; UHDRS: Unified Huntington′s Disease Rating Scale

intru: intrusion; avoid: avoidance; depr: depression; estm: low self-esteem; aggr: aggressive behaviour; obs: obsessions; irrit: irritability

a HD family may all be involved in fluctuating levels of distress in non-carriers (Gargiulo et al. 2009). As reported in other reviews (Broadstock et al. 2000), the majority of included studies explored psychological impact of predictive genetic testing using general measures of affect and emotion; three of the eight appraised in this review employed a measure of behaviour and/or cognition (Larsson et al. 2006; Wahlin et al. 2000; Witjes-Ané et al. 2002). Further research including these measures would allow greater understanding of the full psychological impact of predictive genetic testing on individuals, particularly with regards to the conflicting reports of suicidal ideation reported in two of the reviewed papers.

In all but one of the studies (Gargiulo et al. 2009), clinically significant levels of the constructs under scrutiny were not found. Yet, more detailed qualitative narratives investigating individuals at-risk of HD undergoing predictive genetic testing report distressing emotions such as shock, fear and frustration at both the point of awareness about at-risk status and again with test result (Schwartz, 2010). This raises the question as to whether the measures used were sufficiently nuanced to phenomena or sensitive enough to detect emotional reactions reported by individuals. The lack of clinically significant findings may represent an absence of distress, but may also be an artefact of poor fit of measures.

Illness representations have been argued to be central in how an individual perceives their own physical and mental health, therefore playing a significant role in psychological distress (Arran et al. 2014; Rozema et al. 2009). Models of health psychology and illness representations may be usefully drawn upon to guide future research in developing and applying disease-specific, health-related measures of psychological impact. Such measures are argued to be more sensitive for the detection and quantification of clinically significant changes (Patrick & Deyo, 1989). Health-related measures such as the Health Orientation Scale (HOS, Snell et al. 1991) have been used to assess the psychological impact of being identified as a genetic carrier of familial adenomatous polyposis (FAP, Michie et al. 2001), and disease-specific measures are currently being developed and used to explore the psychological impact of cancer (Zebrack et al. 2006; 2008). Measures such as the Huntington′s Disease Quality of Life questionnaire (HDQoL, Hocaoglu et al. 2012) have attempted to bridge this gap for HD and it is hoped that research will utilise these measures in the future.

Three studies utilised the IES, a standard measure of trauma, and appeared to anticipate the experience of receiving predictive genetic test results as potentially harrowing, although this was not explicitly expressed by the authors. This

may be an understandable orientation for research when outcomes of testing are devastating. Traumatic events are believed to shatter the assumptions an individual holds about themselves, others and the world causing them distress (Janoff-Bulman, 1992). However, from these shattered assumptions personal growth can be achieved through how we relate to others, our sense of self and our life philosophy (Tedeschi & Calhoun, 2004).

Recent evidence suggests such post-traumatic growth can occur following predictive genetic testing for HD, with both carriers and non-carriers reporting greater appreciation for life and enriched relationships (O'Rourke, 2011). Such evidence may mean that assumptions about the adverse psychological impact of predictive genetic testing should be modified, and that more theoretically robust studies, employing measures derived from constructs reflecting growth as well as pathology are warranted. Should future research findings point to a post-traumatic growth response following predictive genetic testing for HD, there may be implications for clinical practice. Evidence from the trauma literature is suggestive of early interventions having negative consequences in psychological well-being (Bisson et al. 1997; Hobbs et al. 1996) whilst later more structured psychological approaches have reduced levels of distress (McNally et al. 2003). This may therefore be suggestive of a need for predictive genetic testing protocols to include monitoring of psychological impact over time with structured approaches offered with the identification of heightened distress.

The current review is suggestive of little psychological impact of predictive genetic testing irrespective of test outcome and may imply that living as a HD gene carrier is not in itself clinically distressing. Qualitative data elicited from HD carriers would offer some support. Identification of carrier status can generate some emotional perturbation and unwanted experiences of decisional regret and adaptation to life and goals. Yet some positive consequences such as greater life appreciation and an appreciation, and increased closeness, of family relationships have been disclosed (Hagberg et al. 2011). Staff who are working with patients as they discuss options for testing may frame discussions more positively if reassured that those who request testing do not inevitably experience adverse psychological impact. However, greater consideration of how this would be introduced is warranted, given concerns have been expressed that non-directive and full disclosure of genetic status for all at-risk individuals is both unrealistic and unwanted (Geller & Holtzman, 1995). A much larger cadre of research understanding the psychological robustness of those choosing not to undergo predictive genetic testing is needed before detailed recommendations are made. This is reflected in the most recent recommendations made to the international guidelines for predictive genetic testing in HD whereby information on consequences of test result has highlighted the negative consequences of undergoing testing, and a focus on individual choice for taking the test is emphasised (MacLeod et al. 2012).

Individuals requesting genetic testing for HD have long been described in the literature as a self-selecting group with resources and coping skills exceeding those who decline (Kessler, 1994). All current reviewed studies have utilised a self-selected sample with potentially biased findings. Indeed, genetic testing protocols and procedures have been recognized to deter all but the most motivated and determined at-risk individuals (Kessler, 1994). Research has suggested that non-testers may demonstrate higher levels of pessimism relating to themselves and their future before testing (van der Steenstraten et al. 1994) and this may serve as a self-fulfilling prophecy causing harm when unfavourable test results are obtained (Konrad, 2003). For other genetic conditions, those who electively remain ignorant of their carrier status appear to benefit from a protective function (Fanos & Johnson, 1995). Furthermore, high drop-out levels recorded in the studies reviewed herein have demonstrated higher levels of hopelessness, intrusion and avoidance, and lower levels of general well-being in non-completing carriers (Timman et al. 2004).

All such findings suggest that greater exploration of both resilience of individuals requesting predictive genetic testing and those opting against it is needed. Achieving consensus on the most appropriate and effective protocols to address psychological impact, support individuals and their families prior to any recommendations for encouraged testing, needs additional research. This should ensure that sampling procedures will need to be adapted potentially utilising respondent-driven sampling methods or survey style questionnaires via the means of non-health related media to target the hard-to-reach population.

This is the first review of the psychological impact of predictive genetic testing by mutation analysis on individuals at-risk of HD which has employed systematic search processes. The eligibility criteria utilised permitted reduction of bias evident in the published literature via mixed genetic testing procedures, allowing the results of the current review to be more salient and generalizable to those currently undergoing predictive genetic testing.

In conducting this review it is acknowledged that predictive genetic testing may have impacts beyond the individual undergoing testing, notably the family system (Sobel & Cowen, 2000). However, for the purpose of this review, consideration of the broader psychosocial impacts would have reduced a focused scrutiny of how the individual being tested is affected given the much larger literature that would be elicited. Given theoretical precedents for an emphasis on individual appraisal of testing and results, a focus at the individual level was felt to be warranted. Clearly broader psychosocial impacts could form the basis of a further review.

Conflict of Interest Statement S Crozier, N Robertson and M Dale declare that they have no conflict of interest.

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