Adversity, Distress and Stress-Function in Clinical and Non-Clinical Voice-Hearers

Baumeister, David

Awarding institution:
King's College London

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Adversity, Distress and Stress-Function in Clinical and Non-Clinical Voice-Hearers

David Baumeister

Department of Psychology

Institute of Psychiatry, Psychology & Neuroscience

King’s College London

This thesis is submitted to the University of London for the degree of Doctor of Philosophy.
Abstract

Background

The present PhD project investigated the role of psychophysiological stress-function and adversity exposure in auditory verbal hallucinations and the clinical status of voice-hearers. Psychosis is associated with several alterations in biological stress systems, including the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis, as well as subjective stress levels and -reactivity. Exposure to childhood trauma has been particularly linked to the emergence of auditory verbal hallucinations in psychosis, as well as a dysregulation of stress-psychophysiology. However, it remains unclear whether changes in stress-function and -reactivity are related to auditory hallucinations specifically, or only to psychosis more generally. Further, auditory verbal hallucinations occur in both clinical and non-clinical populations. Voices in healthy and clinical voice-hearers share many characteristics, including phenomenological (such as loudness) and neurophysiological correlates of auditory verbal hallucinations. However, healthy voice-hearers do not experience distress in response to their voices, and their voices contain less negative content. It remains unknown whether psychophysiological stress-function may also discriminate clinical and non-clinical voice-hearers, and whether dysregulated stress-function is associated with the experience of hearing voices, and/or need for care. Evidence suggests there is increased childhood trauma exposure in healthy voice-hearers, at similar rates to clinical voice-hearers. However, adolescence/adulthood adversity remains largely unexplored in healthy voice-hearers, as does exposure to other risk factors including socioeconomic adversity and substance use. A more recent version of the diathesis-stress model, the three hit model, has highlighted the role of adversity after childhood in shaping pathological trajectories, which may partially explain the difference in distress and need for care in clinical and healthy voice-hearers. Lastly, it is not known whether, and to what degree, voice content contributes to
psychophysiological dysregulation in clinical voice-hearers. To address these issues, the present project investigated three key research questions:

1. Does adolescent/adulthood adversity exposure differ between healthy voice-hearers and clinical voice-hearers, and is the differential adversity exposure associated with increased stress-sensitivity?
2. Does the content of voices exacerbate stress-reactivity?
3. Does psychophysiological stress-function in clinical voice-hearers differ from those of healthy voice-hearers and healthy controls without voices?

Methods

Three individual studies are reported to assess these research questions:

1. A cross-sectional study of clinical and healthy voice-hearers was carried out to assess the role of familial risk and adversity exposure in childhood, and adolescence/adulthood in the context of the three hit model. Further, the association of adversity exposure with perceived stress was examined.

2. A cross-sectional design with a healthy non-voice hearing sample was carried out using simulated auditory hallucinations with negative and neutral content to assess their impact on psychophysiological stress-reactivity during psychosocial stress exposure. The potential buffering effects of mindful appraisals of voices on psychophysiological stress-reactivity were also assessed.

3. A cross-sectional study of clinical and healthy voice-hearers, as well as a healthy control group with no voices, was carried out comparing the three groups on diurnal HPA and ANS activity, HPA response to pharmacologically induced negative feedback, and HPA
Results

The cross-sectional study on adversity exposure showed that, unexpectedly, victimisation and discrimination experiences were similar in clinical and healthy voice-hearers in both childhood and adolescence/adulthood. However, the two groups differed on familial psychosis risk, adolescence/adulthood socioeconomic status, and substance use, with the clinical group reporting greater rates of adversity exposure. These variables were further predictive of perceived stress, after controlling for group. The analogue voice study demonstrated that negative voices exacerbated subjective, but not physiological, stress-reactivity, compared to neutral voices and ambient sounds. Having a mindful stance towards the voices during the task was associated with lessened stress-reactivity. Finally, as predicted, clinical voice-hearers showed several indices of aberrant psychophysiological stress-function of the HPA axis, compared to both healthy voice-hearers and controls without voices, although not always in the predicted direction. Contrary to our predictions, there were no differences between groups on parameters of the ANS. However, there was some evidence to suggest stress-function in healthy voice-hearers also diverges from non-voice-hearing controls on some HPA parameters, including reduced cortisol levels during stress exposure, slower speed of cortisol recovery from the stressor, and lower HPA negative feedback capacity.

Conclusion

The present thesis found evidence to suggest that specific types of adversity exposure and stress-function are related to the need for care of clinical voice-hearers and may be involved in pathological outcomes of voice-hearing. Differential adversity exposure, and its relationship to
stress-sensitivity may therefore partially relate to psychopathological trajectories in voice-hearing. The negative content of voices may further contribute to the maintenance of need for care through exacerbated stress-reactivity. Finally, dysregulated psychophysiological stress-function is present in clinical voice-hearers, and partially discriminates them from healthy voice-hearers. Overall, the present findings identified specific potential psychophysiological markers of risk and resilience in auditory verbal hallucinations and need for care. This thesis provides an initial stepping stone for future research developments to explore precise causal and mechanistic relationships of adversity exposure, psychophysiological stress-function and need for care in voice-hearing.
Acknowledgements

“What goes on inside is just too fast and huge and all interconnected for words to do more than barely sketch the outlines of at most one tiny little part of it at any given instant.”

- David Foster Wallace

All these acknowledgments, and really the entire thesis, should be considered with this obvious yet treacherous complication (so aptly described by David Foster Wallace) in mind.

I first wish to acknowledge my supervisors, Dr Emmanuelle Peters, Prof Paul Chadwick and Prof Oliver Howes, who have been tremendous in their contribution to this research project, as well my academic development. I was entrusted to substantially shape my PhD research, whilst also receiving their expertise and guidance when needed, and the chance to work on a research topic bridging so many of my academic interests has been a privilege. In extension, I wish to acknowledge my funders, the Medical Research Council and King’s College London, as well as the KCL Psychology Department for hosting this project. I specifically wish to highlight my gratitude to Emmanuelle, who has been nothing but fantastic and who maintained her open-door policy despite my frequent waltzing into her office with some great new idea to discuss or some massive fire to extinguish.

None of this would have been possible without the relentless support and love of my parents, Evi and Markus, and Norbert (don’t ask, it’s complicated), and my brother Julius. My work here certainly makes me recognise aspects of each of them and carries their fingerprint in myriad ways. Also, I hope this whole PhD jazz makes up for all the tattoos. Talking of which – I want to thank Chris, who has remained my best friend despite all these years of my absence, and few things in my life are greater than stepping off the plane and acting like I never left the country. Similarly, I’d like to thank old comrades like Kristina and Anton for their ongoing friendship.
I would further wish to acknowledge colleagues, peers and friends I have met along my journey. Starting with the original lunch group, I want to thank Clem for her somewhat stoic advice on my first days and friendship since then. Similarly, Otts has been a great friend and deserves to hold her head up in pride (aided by the weirdly ‘cushioned’ back of her head). Xtina deserves my gratitude for frequently keeping me sane by reminding me there are people doing fMRI in dogs. Finally, I’m very grateful to Toby Wise for being a great friend and having an ever-available advice hotline (“Toby, can you explain all of SPM to me in an hour?”). Further thanks go to the noteworthy Toby Pillinger, who not only frequently brightened my days by sheer hilarity but also aptly counselled my participants and defied any croquet-related difficulties. Nina – thank you “for help that can’t be described eloquently”. In so many ways. My thanks also go to Simon, who always made sure that working out would be more stressful than my work. I also owe gratitude to other colleagues and collaborators who have been incredibly supportive along the way, including Karlijn, Alice, Valeria, Jens P., G-Nan, Tracy and Suzanne. I’m sorry the word count is too tight for more personal quips for each of you, and apologies to anyone I may have forgotten.

I would further like to thank a certain Folkestone resident whose generosity has been invaluable to my recruitment. Lastly, my academic skills and passions have been forever shaped by the honourable circle of elders. Long live the elders, you know who you are.

Last, yet by no means least, I wish to thank my participants. Particularly my clinical participants have made practical aspects of carrying out this research fascinating, meaningful and heart-warming. Signing up for a study with the word ‘stress-reactivity’ in the title is testament to admirable altruism and selflessness, and for those who face distress far more severe than most of us can imagine it shows a spirit of charity that has left me in awe. I humbly hope that my work can help and repay, somehow, someday. I cannot thank you enough for this journey.

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<td>Mean</td>
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<td>mg</td>
<td>Milligram</td>
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<td>Mineralocorticoid Receptor</td>
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<td>NF-kB</td>
<td>Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells</td>
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<td>nmol/L</td>
<td>Nano Mole Per Litre</td>
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<td>Post-Traumatic Stress Disorder</td>
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<td>PVN</td>
<td>Paraventricular Nucleus</td>
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<tr>
<td>RSA</td>
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<td>SAM</td>
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<td>Scale for The Assessment Of Positive Symptoms</td>
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<td>UNIQUE</td>
<td>Unusual Experiences Inquiry</td>
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<td>Visual Analogue Scale</td>
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<td>VPDS</td>
<td>Voice Power Differential Scale</td>
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<td>VT</td>
<td>Vagal Tone</td>
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<td>WAIS-III</td>
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Chapter 1 – Thesis Rationale and Outline

The primary aim of the present PhD project was to investigate the role of psychophysiological stress-function, distress and adversity exposure in voice-hearing, and how it relates to the clinical status of voice-hearers. Psychosis frequently presents with distressing auditory verbal hallucinations, as well as disruption of physiological and subjective stress-regulation. The aetiology of auditory verbal hallucinations (AVHs) in psychosis appears closely linked to stress-exposure (Bentall, Wickham, Shevlin, and Varese, 2012), and there is emerging evidence that psychosis may be causally linked to childhood trauma (Read, van Os, Morrison, and Ross, 2005; Varese et al., 2012). Psychosis is further characterised by increased threat perception (Underwood, Kumari, and Peters, 2016), subjective stress-reactivity (Reininghaus et al., 2016) and aberrant activity of the body’s stress systems (Borges, Gayer-Anderson, and Mondelli, 2013; Bradley and Dinan, 2010; Ciufolini, Dazzan, Kempton, Pariante, and Mondelli, 2014; Montaquila, Trachik, and Bedwell, 2015). However, the dysregulation of psychophysiological stress-function specifically in relation to AVHs remains largely unexplored.

Although initially classified as a “first-rank” symptom of schizophrenia (Schneider, 1959), AVHs have increasingly been recognised in significant proportions of healthy individuals with no need for care. Healthy voice-hearers (HVHs) are individuals who experience persistent auditory verbal hallucinations, yet without suffering the significant distress this experience may cause in psychosis patients (clinical voice-hearers; CVHs), and with no discernable need or desire for clinical intervention. Indeed, for some of these individuals, the experience of hearing voices is regarded as positive, meaningful and life-enriching (Johns et al., 2014). Not only has this “discovery” of HVHs fundamentally questioned the diagnostic value of AVHs, but they may also be a study population of crucial value to the understanding and treatment of AVHs in a clinical context. To ascertain the similarities and differences between HVHs and CVHs, and the
implications for the psychosis continuum, a systematic review of the HVH literature was conducted in Chapter 2.

As identified by the systematic review, several issues in HVHs relating to stress-function have not been addressed to date. First, the existing literature strongly suggests that childhood trauma in CVHs and HVHs is significantly more prevalent than in HCs (Daalman et al., 2012b; Johns et al., 2014). However, the literature on HVHs has not investigated exposure to victimisation in adult life, or to other risk factors such as substance misuse or socio-economic disadvantage, which may have an impact on the outcome of AVHs. According to the three hit model of stress and resilience, genetic predisposition, early life experiences and later-life environment interact in the aetiology of stress-related mental disorders (Daskalakis, Bagot, Parker, Vinkers, and de Kloet, 2013). To address whether differential adversity exposure at specific developmental stages may account for need for care status of voice-hearers, a cross-sectional comparison of adversity exposure in a sample of CVHs and HVHs was undertaken in Chapter 4. In this study, we compared CVHs and HVHs on measures of familial incidence of mental illness, victimisation and discrimination exposure and socioeconomic status up to age 13, and victimisation, discrimination, as well as socioeconomic status and substance misuse in adolescence and adulthood. Further, we investigated the association of these variables with stress-sensitivity (i.e., perceived stress in everyday life) after controlling for clinical status.

While the systematic literature review of healthy voice-hearers highlighted many similarities in the phenomenology of AVHs in CVHs and HVHs (e.g., number of voices or perceived location), it also showed that there are differences on other parameters, such as frequency and voice content. CVHs mainly hear negative and derogatory voices, and HVHs hear primarily neutral or positive voices (Johns et al., 2014). Such differences in voices may partially account for differential voice-distress. To assess whether AVHs and their content impact on stress-reactivity,
an experimental paradigm was carried out in Chapter 5. Healthy individuals with no AVHs underwent a psychosocial stress paradigm whilst being exposed to simulated AVHs with different content, to assess the degree to which voice content may drive subjective and physiological stress dysregulation. Participants in this study were randomly allocated to either negative voices, neutral voices, or non-voice ambient sounds, and their subjective stress response as well as HPA- and ANS-response were assessed. The potentially moderating effects of mindful appraisals of the simulated voices on stress-reactivity were also examined.

As reviewed in Chapter 3, dysregulation of the neuroendocrine and nervous stress systems is detrimental to physical as well as psychological well-being (Baumeister, Lightman, and Pariante, 2014; McEwen, 2008), and has been implicated in the aetiology and pathophysiology of psychosis (Bradley and Dinan, 2010; Pruessner, Cullen, Aas, and Walker, 2017). Thus, a potential substrate of the clinical divergence of HVHs and CVHs may be found in compromised integrity of the body’s systems dedicated to dealing with stress. To address the question of whether physiological stress-function is divergent between CVHs and HVHs, a detailed assessment of neuroendocrine and autonomic nervous system function was conducted in CVHs, HVHs and healthy controls in Chapter 6. In this study, we assessed unstimulated baseline activity of the HPA-axis and ANS over the course of one day, measured negative feedback capacity of the HPA-axis, and assessed subjective, HPA and ANS responses to an acute psychophysiological stressor. To our knowledge, it is the first study to investigate stress-function specifically in relation to AVHs, and through the addition of a HVH sample allows for differentiation of findings relating to AVHs in general, or specifically to AVHs and need for care. The overall conclusions, strengths and limitations, implications and directions for future research of the present thesis are discussed in Chapter 7.
Chapter 2 – Auditory Verbal Hallucinations and Continuum Models of Psychosis: A Systematic Review of the Healthy Voice-Hearer Literature


2.1 Introduction

There is accumulating evidence that the experience of auditory verbal hallucinations (AVHs) is not uncommon in healthy individuals, and is not necessarily an indicator of psychopathology. A significant proportion of healthy individuals experience psychosis-like symptoms such as voice-hearing at some point in their lives; usually AVHs present as transient experiences, for example during childhood and adolescence, periods of bereavement or in the form of hypnagogic or hypnopompic false auditory perceptions (de Leede-Smith and Barkus, 2013). A recent meta-analysis estimated a median prevalence of 6% and median incidence of 1.2% of hallucinatory experience in the general population (Linscott and van Os, 2012). Notably, Linscott and van Os’ (2012) meta-analysis found that 20% of those who report psychotic experiences (including other phenomena such as delusional beliefs) go on to experience them persistently, 7.4% in the context of a psychotic disorder. These rates may be similar for AVHs specifically, as a recent cohort study of 1,912 adolescents found that of the 5% who reported auditory hallucinations at baseline, they were still present in 27% two years later (De Loore et al., 2011). The term ‘healthy voice-hearers’ (HVHs) has been coined to describe individuals who experience persistent auditory verbal hallucinations, yet have no need for clinical care and do not suffer the significant distress this experience may cause in clinical populations (‘clinical voice-hearers’; CVHs).
However, there remains uncertainty over how the two populations are related. The present systematic review aims to address such conceptual difficulties and provide a comprehensive overview of the currently available evidence.

The recent focus on AVHs in the healthy general population has arisen from a wider reconceptualisation of psychosis and a shift from diagnostic to symptom-focused approaches. Classically, AVHs were defined as first-rank symptoms of schizophrenia (Schneider, 1959), as part of discrete, categorical models, i.e. those employed by diagnostic classification systems (Table 2.1; Model 1). However, these diagnostic models, although still employed in clinical practice, have been criticised for their lack of an empirical evidence-base (Bentall, 2004; Kaymaz and van Os, 2010; Linscott and van Os, 2010; van Os, 2009). Transdiagnostic, symptom-focused approaches have been proposed both for psychosis (e.g., the transdiagnostic psychosis spectrum; Reininghaus and van Os, 2016) as well as wider mental health (e.g., the Research Domain Criteria project; Insel et al., 2010). AVHs are present in a range of mental health difficulties, including depression and anxiety, post-traumatic stress disorder, emotionally unstable personality disorder, and obsessive-compulsive disorder (Johns et al., 2014; Upthegrove et al., 2016; van Os and Reininghaus, 2016). Further, the impact and presentation of AVHs may differ within individuals in need for care, and there have been proposals to subtype AVHs in clinical research and practice (Smailes, Alderson-Day, Fernyhough, McCarthy-Jones, and Dodgson, 2015).

Conceptually, there has also been a marked shift from categorical models towards a continuum view of psychotic symptoms and anomalous experiences that extends not just across diagnostic categories but also into the (healthy) general population. This has long been proposed by researchers such as Claridge (1994) and Bentall (2004), and has gained considerable epidemiological support (Linscott and van Os, 2013; Linscott and van Os, 2010; van Os, Linscott,
According to the continuum model, HVHs are situated on a continuous dimension between CVHs and non-voice-hearing healthy individuals (healthy controls; HCs) in terms of their anomalous experiences, but without crossing the threshold for need for care. However, different conceptualisations of the continuum model exist in the literature (see Table 2.1; models 2 and 3). Claridge (1994; Siever and Claridge, 2002) has differentiated between ‘quasi-dimensional’ (Table 2.1; Model 2) and ‘fully dimensional’ (Table 2.1; Model 3) models. In the former, the continuum describes disease severity; it is assumed that psychotic experiences and distress are part of the same dimensions and that psychotic experiences are ultimately indicative of a psychobiological abnormality but simply in attenuated form. It is further assumed that only a small proportion of the general population has a predisposition for such experiences. In a fully dimensional model, however, the continuum of anomalous experiences may be largely independent from the continuum of clinical distress or need for care, and makes no prediction regarding the outcome of psychotic experiences. The propensity for such experiences is distributed in the general population as part of normal individual differences and only in extreme forms necessitates care. Such a conceptualisation is more in line with viewing voice-hearers without need for care as being truly “healthy”, rather than merely “subclinical”.

However, these conceptualisations may still be over-simplistic (Kaymaz and van Os, 2010; Linscott and van Os, 2010). Linscott and van Os (2010) carried out a systematic review and meta-analysis of primarily epidemiological data on what they refer to as the ‘extended phenotype model’. Their results suggest that there is evidence for continuity of symptoms, based on the high incidence and prevalence rates of psychotic experiences in the general population compared to the actual rate of clinical psychotic disorders. However, they also found evidence for a dichotomous distribution of individuals who have a liability to schizotypal traits from individuals who do not. These mixed findings suggest the possibility that the psychosis
continuum may encompass two latent, discontinuous subgroups, leading to a hybrid conceptualisation of quasi- and fully-dimensional models. Current evidence further suggests that psychosis is a complex multifactorial construct, with individual symptoms or characteristics: a) lying on individual continua (Russo et al., 2014; van Os, 2009); b) showing differing prevalence rates and causal factors (Wigman et al., 2011b; McGrath et al., 2015); c) having differing implications for a need for care or clinical risk (Wigman et al., 2011b; Kaymaz et al., 2012); and d) demonstrating varying correlational or predictive relationships with other symptoms (Wigman et al., 2011a; Bell et al., 2008). Most recently, van Os and Reininghaus (2016) have proposed a transdiagnostic psychosis spectrum in which psychotic symptoms in the general population are continuous with clinical psychotic disorders, but can nonetheless present independently. This conceptualisation encompasses both specific psychosis factors (e.g., positive symptoms) as well as nonspecific associations with psychopathology (e.g., affective dysregulation), and the combination of these two underlying constructs then becomes critical in leading to a need for care.

In an editorial aiming to stimulate the continuum debate, David (2010) suggests that the continuum hypothesis should be taken as the null hypothesis, and the present review examines whether there is evidence to refute it in relation to AVHs specifically. The focus on AVHs allows investigation of the psychosis continuum in the context of a specific phenomenon of the psychosis dimension that presents both across health-pathology and across different types of pathology. Assessing whether the available research on HVHs has produced results congruent with the current evidence on the psychosis continuum can attest to its relevance and add to its validity. Indeed, Johns and colleagues (2014) call on research to investigate the role of the quasi- and fully-dimensional continua in AVHs in healthy individuals. In turn, the psychosis continuum models provide an important context to determine to what extent HVHs are “healthy” and are likely to remain so. For instance, whilst HVHs may present as currently healthy, the
transdiagnostic extended phenotype model presented by van Os and Reininghaus (2016) notes the temporal continuity of psychotic experiences with clinical disorders, i.e., HVHs may be at greater risk of psychotic disorders long-term. Furthermore, examination of the relationships between AVHs in healthy populations and other symptom dimensions and characteristics relevant psychosis, such as affective difficulties, risk factors, or neurobiological substrates, may be valuable for the understanding of AVHs and need for care in clinical populations.
Table 2.1 – Model conceptualisations and hypotheses

<table>
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<th>Model conceptualisation</th>
<th>Model hypotheses</th>
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| **Model 1: Diagnostic discontinuous model** | - HVHs differ from HCs on almost no parameters, indeed HVH should not be identifiable as a separate group  
- AVHs in HVHs cannot be explained in such a model, and those experiences are likely highly dissimilar from those in CVHs |
| **Model 2: Quasi-dimensional model** | - HVHs form a middle-point between CVHs and HCs on almost all parameters  
- AVH parameters (e.g. frequency) in HVHs are consistently lower than in CVHs, i.e. present in an attenuated form  
- Occurrence of psychotic experiences is directly related to distress/need for care |
| **Model 3: Fully dimensional model** | - AVHs should occur unrelated to distress in HVHs  
- Parameters not related to AVHs will vary at random, HVHs do not differ from HCs in need for care  
- Occurrence of psychotic experiences is not necessarily related to distress/need for care |

Note: Vertical shading indicates mental well-being or the absence of need for care, horizontal shading indicates psychological difficulties and need for care, and grid shading indicates the occurrence (e.g., frequency, intensity) of psychotic experiences.
Whilst the reviewed continuum conceptualisations relate to psychosis or schizotypal personality traits across the wider population, rather than the specific phenomenon of auditory hallucinations, their relevance to AVHs in healthy individuals is inferred here. Similarly, whilst still relevant, many studies in the HVH literature were not carried out with the continuum hypothesis in mind and are thus integrated into an overarching framework to consider this literature. According to the diagnostic model, benign AVHs should be highly dissimilar as an experience to those found in CVHs, and HVHs and HCs should be indistinguishable on almost all parameters (e.g., risk factor exposure). According to the quasi-dimensional model, HVHs will be on a middle-point between CVHs and HCs on almost all parameters, including need for care and voice-distress. In such a model, increases in the occurrence of psychotic experiences would be associated with increased need for care. Lastly, a fully-dimensional model would predict that the occurrence of AVHs is largely unrelated to need for care, and HVHs should not be at greater risk of distress than HCs. Other parameters should vary at random. However, according to the more recent epidemiological conceptualisation of extended, transdiagnostic phenotypes with latent subgroups, the available evidence would be expected to support both quasi- and fully-dimensional models to a similar degree. Thus, the present review has two main hypotheses: firstly, the evidence will be incompatible with the diagnostic model; secondly, the evidence will provide support for both quasi- and fully-dimensional models, depending on methodology used and sample characteristics of the study.

Several narrative reviews have been published on AVHs in healthy populations (Badcock and Chhabra, 2013; Badcock and Hugdahl, 2012; de Leede-Smith and Barkus, 2013; Johns et al., 2014; Larøi, 2012). However, these tend to be broader (e.g. inclusive of prodromal populations), or more theoretical or narrow in their discussion (e.g. of neurocognitive mechanisms) than the focus of the present review. Moreover, by their narrative nature, they are more vulnerable to bias than the systematic approach undertaken here. The present systematic review aims to: give
a comprehensive overview of the phenomenon of persistent AVHs in healthy adult populations; consider the evidence for models of the psychosis continuum in the context of AVHs; and identify areas where future research is needed.

2.2 Methods

2.2.1 Search Strategy

A systematic review of the literature was performed using PsycINFO, EMBASE, and Medline for the subject headings “auditory hallucination*” and “voice hear*” cross-referenced separately with the terms “healthy”, “no need for care” and “non-clinical”. The literature review was performed in February 2016. Articles were limited to research in human participants, and published in English language. The initial search produced 230 on PsycInfo, 346 on Embase and 161 on Medline (see Figure 2.1). Additionally, 17 papers were identified through search of references in identified papers. One additional paper was identified through personal communication with the authors (Jacobsen et al., Under Review). The following criteria were used for exclusion and inclusion into the review:

Exclusion criteria:

- Only voice-hearers with a clinical diagnosis of a psychotic disorder or other conditions associated with AVHs (e.g. PTSD, epilepsy)
- Only hallucination-proneness assessed (e.g. Launay-Slade Hallucination Scale (LSHS; Launay and Slade, 1981) scores) and no reporting of current AVHs
- Childhood and adolescent samples
- General assessment of anomalous experiences only
- Elicited hallucinatory experiences (e.g. signal detection tasks or through hypnosis)
- Drug-induced hallucinations
- Non-verbal hallucinations
Inclusion criteria:

- Studies with a sample of individuals without clinical diagnoses who report hearing voices but no related distress
- Articles published in English language

2.2.2 Selection

After exclusion of duplicates, articles not published in English language, and studies not including human participants, 398 article titles and abstracts were scrutinised for inclusion into the review. Seventy appropriate articles were identified for full-text analysis, of which 36 met criteria for inclusion. Full-text analysis and data extraction were carried out independently by two authors, and any inconsistencies were discussed until consensus was reached. Notably, several of the identified studies (from the Dutch (Utrecht) group, marked in Table 2.2) included the same or overlapping samples, however often with slightly different numbers of participants and different main outcome measures. Ineligible articles (n = 34) were excluded for the following reasons: only hallucination proneness/anomalous experiences measured (n = 17); only elicited hallucinations measured (n = 10); adolescent sample (n = 3); only assessment of non-wakeful hallucinations (n = 1); hallucinations in epilepsy sample (n = 1); no stratification for need for care (n = 2) (see Figure 2.1). Studies where samples were selected purely on the basis of proneness to hallucinations (e.g., using a total score on the LSHS) were excluded as such measures may include a) non-AVH hallucinations and b) transient experiences. However, studies that used individual AVH-specific LSHS items (e.g., “In the past I have had the experience of hearing a voice and then found no one was there”) as part of their inclusion criteria were included (see Table 2.2), if they satisfied the criterion of ‘reporting of current AVHs’.

Study characteristics are presented in Table 2.2. The results presented below are organised with a focus on specific characteristics that have emerged from the literature, rather than by their
congruence with the explanatory models evaluated here, which is returned to in the discussion. The structure of the results is aimed at aiding the reader interested in discrete aspects of HVH research, and improving reading experience and accessibility. Results are presented by the following characteristics: voice phenomenology, their impact and appraisal, mood disturbances, impairment and functioning, related psychotic phenomena, cognitive functioning, neuroimaging, trauma exposure and familial risk.

Figure 2.1 – PRISMA diagram of search strategy
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Group characteristics</th>
<th>AVH Selection</th>
<th>Mean Age</th>
<th>% Female</th>
<th>Measures</th>
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<tbody>
<tr>
<td>1. Andrew et al., 2008</td>
<td>22 CVHs 21 HVHs</td>
<td>CVHs were recruited from mental health services, HVHs were recruited from spiritualist sources. Psychiatric status in HVHs was not formally assessed and meeting criteria for a psychiatric diagnosis was not amongst the exclusion criteria. Anyone with an organic condition that may cause AVHs was excluded.</td>
<td>Participants were self-selected for experiencing &quot;clairaudience&quot;. Presence of AVHs was assessed via PSYRATS but was not a formal part of selection procedures.</td>
<td>CVHs: 39.6  HVHs: 50.7</td>
<td>CVHs: 40.9  HVHs: 71.4</td>
<td>- Psychotic Symptoms Rating Scale Auditory Hallucinations Subscale - Beliefs About Voices Questionnaire - Revised - Post-Traumatic Diagnostic Scale - Impact of Events Scale - Beck Anxiety Inventory - Beck Depression Inventory - II</td>
</tr>
<tr>
<td>2. Beavan and Read, 2010</td>
<td>84 CVH 69 HVH (collapsed sample)</td>
<td>Clinical status was assigned by stratifying for mental health service contact.</td>
<td>Self-selected individuals who responded to having &quot;heard voices that no one else can hear&quot;.</td>
<td>48.0¹</td>
<td>66.0¹</td>
<td>- Hearing Voices Questionnaire - Qualitative interview</td>
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<td>3. Begemann et al. 2015*</td>
<td>101 HVH 101 HC</td>
<td>As Daalman et al., 2011a</td>
<td>As Daalman et al., 2011a</td>
<td>n/a</td>
<td>n/a</td>
<td>- Stroop Color-Word Task - WAIS-III - Childhood Trauma Questionnaire</td>
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<td>Study</td>
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| Cottam et al., 2011 | 15 C-CVH 14 NR-CVH 20 C-HVH | HVH-Cs were recruited from churches. They were not formally assessed for psychiatric status. CVHs were recruited from mental health services. | Participants were included if they endorsed the LSHS item "In the past I have had the experience of hearing a voice and then found no one was there". | CVH-C: 41.8 CVH-NR: 41.0 HVH-C: 52.7 | CVH-C: 20.0 CVH-NR: 21.0 HVH-C: 60.0 | - Launay-Slade Hallucination Scale  
- Topography of Voices Rating Scale  
- Affective Experiences Questionnaire  
- Cognitive Assessment of Auditory Hallucinations (supplemented with questions for religious belief and interpretation) |
<table>
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<th>Study</th>
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| 5. Daalman et al., 2011a* | 118 CVH 111 HVH | HVHs were excluded if they met criteria for a DSM-IV diagnosis other than depressive or anxiety disorders in complete remission. Individuals were screened for illegal substance use via urine samples, and alcohol or drug abuse in the last 3 months led to exclusion. HVHs were recruited online; CVHs were recruited from mental health services. CVHs consisted of patients with schizophrenia, schizoaffective disorder and psychosis not otherwise specified. | Participants were initially screened with LSHS items concerning having heard a person's voice when no-one was there and having been troubled by voices in their head. Voices had to be distinct from thoughts and have a perceptual quality, minimum frequency for AVHs in HVHs was once per month and minimum duration since onset was 1 year. | CVH: 36.6  HVH: 41.5 | CVH: 40.0 HVH: 71.0 | - Psychotic Symptoms Rating Scale Auditory Hallucinations Subscale  
- Structured Clinical Interview for DSM-IV II - Personality Disorders  
- Comprehensive Assessment of Symptoms and History |
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<th>Study</th>
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| 6. Daalman et al., 2011b* | 101 HVH 101 HC | As in Daalman et al, 2011a. All participants had an IQ of 80 or above. | As Daalman et al., 2011a, except minimum frequency of AVH was once every 3 months for at least 1 year. | HVH: 43.8 HC: 43.3 | HVH: 66.3 HC: 70.3 | - Psychotic Symptoms Rating Scale Auditory Hallucinations Subscale  
- Stroop Color-Word Task  
- Wechsler Adulthood Intelligence Scale III subtasks (backward digit span-task, forward digit span-task, vocabulary test, similarities test)  
- California Verbal Learning Test  
- Complex Figure of Rey-Osterrieth  
- Controlled Oral Word Association Test  
- Semantic Fluency Test  
- National Adult Reading Test  
- Raven's Advanced Progressive Matrices  
- Structured Clinical Interview for DSM-IV II - Personality Disorders  
- Comprehensive Assessment of Symptoms and History |
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| 7. Daalman et al., 2012a*    | 40 CVH | As Daalman et al., 2011a | As Daalman et al., 2011a | CVH: 37.6  
HVH: 47.6  
HC: 45.0 | CVH: 47.5  
HVH: 60.0  
HC: 55.0 | - Psychotic Symptoms Rating Scale Auditory Hallucinations Subscale  
- Launay-Slade Hallucination Scale  
- Semantic Expectation Task  
- Structured Clinical Interview for DSM-IV II - Personality Disorders  
- Comprehensive Assessment of Symptoms and History |
| 8. Daalman et al., 2012b*    | 100 CVH | As Daalman et al., 2011a | As Daalman et al., 2011a | CVH: 38.0  
HVH: 42.4  
HC: 43.1 | CVH: 56.0  
HVH: 67.7  
HC: 67.7 | - Psychotic Symptoms Rating Scale Auditory Hallucinations Subscale  
- Childhood Trauma Questionnaire  
- Structured Clinical Interview for DSM-IV II - Personality Disorders  
- Comprehensive Assessment of Symptoms and History |
| 9. Daalman et al., 2013*     | 72 CVH | As Daalman et al., 2011a | As Daalman et al., 2011a, except minimum frequency of AVH was once every 3 months for at least 1 year. | CVH: 39.7  
HVH: 47.6  
HC: 45.1 | CVH: 54.2  
HVH: 69.4  
HC: 72.2 | - Psychotic Symptoms Rating Scale Auditory Hallucinations Subscale  
- Cognitive Biases Questionnaire for Psychosis  
- Structured Clinical Interview for DSM-IV II - Personality Disorders  
- Comprehensive Assessment of Symptoms and History |
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<tr>
<td>10. Daalman et al., 2016*</td>
<td>81 HVH  49 HC</td>
<td>As Daalman et al., 2011a; 5-year follow-up (thus healthy status may not apply)</td>
<td>As Daalman et al., 2011a</td>
<td>n/a</td>
<td>n/a</td>
<td>- Psychotic Symptoms Rating Scale Auditory Hallucinations Subscale</td>
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<td>- Comprehensive Assessment of Symptoms and History</td>
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<tr>
<td>11. Davies et al., 2001</td>
<td>18 CVH  17 C-HVH 12 C-HC 15 NR-HVH 40 NR-HC</td>
<td>Evangelical groups reported being born-again Christians or members of evangelical Christian churches, and reported no previous treatment for mental illness. No evangelical Christians were in the CVH group. All CVHs had a diagnosis of schizophrenia.</td>
<td>Participants were included in voice-hearer groups if they endorsed the LSHS item &quot;In the past I have had the experience of hearing a voice and then found no one was there&quot;.</td>
<td>CVH: 32.6  E: 33.3  NR: 33.0</td>
<td>CVH: 61.1  E: 69.0  NR: 63.6</td>
<td>- Launay-Slade Hallucination Scale - Affective Experiences Questionnaire - Perceptions of Voices Questionnaire</td>
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<td>Study</td>
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| 12. De Weijer et al., 2013* | 35 CVH | As Daalman et al., 2011a CVH group reported AVH at least once an hour. | As Daalman et al., 2011a | CVH: 39.6  
HVH: 42.1  
HC: 41.4 | CVH: 60.0  
HVH: 62.9  
HC: 61.1 | - Psychotic Symptoms Rating Scale Auditory Hallucinations Subscale (items for frequency, emotional valence, distress and control)  
- Positive and Negative Syndrome Scale  
- Global Assessment of Functioning Scale  
- Schizotypal Personality Questionnaire (HVH & HC only)  
- Diffusion Tensor Imaging  
- Magnetisation Transfer Imaging  
- Comprehensive Assessment of Symptoms and History  
- Edinburgh Handedness Inventory |
| 13. Diederen et al., 2010* | 35 CVH | As Daalman et al., 2011a | As Daalman et al., 2011a | CVH: 43.6  
HVH: 44.3  
HC: 41.7 | CVH: 68.6  
HVH: 68.6  
HC: 65.7 | - Psychotic Symptoms Rating Scale Auditory Hallucinations Subscale  
- Positive and Negative Syndrome Scale  
- Global Assessment of Functioning Scale  
- BOLD fMRI during paced verbal fluency task  
- Structured Clinical Interview for DSM-IV II - Personality Disorders  
- Comprehensive Assessment of Symptoms and History  
- Schizotypal Personality Questionnaire |
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| 14. Diederen et al., 2012* | 21 CVH 21 HVH | As Daalman et al., 2011a | As Daalman et al., 2011a | CVH: 34.0  HVH: 46.5 | CVH: 81.0  HVH: 76.2 | - Psychotic Symptoms Rating Scale Auditory Hallucinations Subscale  
- Positive and Negative Syndrome Scale  
- Global Assessment of Functioning Scale  
- Schizotypal Personality Questionnaire  
- BOLD fMRI during AVHs (indicated by balloon squeezes)  
- Structured Clinical Interview for DSM-IV II - Personality Disorders  
- Comprehensive Assessment of Symptoms and History |
| 15. Diederen et al., 2013* | 25 HVH 25 HC | As Daalman et al., 2011a | As Daalman et al., 2011a | HVH: 41.6  HC: 39.8 | HVH: 72.0  HC: 72.0 | - Global Assessment of Functioning Scale  
- Schizotypal Personality Questionnaire  
- BOLD fMRI during resting-state  
- Structured Clinical Interview for DSM-IV II - Personality Disorders  
- Comprehensive Assessment of Symptoms and History |
| 16. Fleming and Martin, 2009 | 19 HVH 102 HC | Mental health practitioners. | Convenience sample was assessed on the prevalence of psychotic symptoms using the PSYRATS | - | - | - Hospital Anxiety and Depression Scale  
- Psychotic Symptoms Rating Scale |
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Group characteristics</th>
<th>AVH Selection</th>
<th>Mean Age</th>
<th>% Female</th>
<th>Measures</th>
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<tr>
<td>17. Hill et al., 2012</td>
<td>20 CVH</td>
<td>HVHs were recruited from spiritualist sources and opportunity sampling. CVHs were recruited from mental health services, HC were recruited via opportunity sampling. None of the HVHs or HCs had a psychiatric diagnosis or were receiving treatment.</td>
<td>Presence of AVHs was assessed via PSYRATS.</td>
<td>CVH: 36.2</td>
<td>CVH: 65.0</td>
<td>- Positive and Negative Syndrome Scale</td>
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<td></td>
<td>20 HVH</td>
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<td></td>
<td>HVH: 39.2</td>
<td>HVH: 60.0</td>
<td>- Psychotic Symptoms Rating Scale Auditory Hallucinations Subscale</td>
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<td></td>
<td>20 HC</td>
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<td></td>
<td>HC: 37.4</td>
<td>HC: 50.0</td>
<td>- Meta-Cognitive Questionnaire (Short Version)</td>
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<td>18. Honig et al., 1998</td>
<td>33 CVH</td>
<td>HVHs were included if they had no previous psychiatric history. CVHs were recruited from mental health services, HVH were recruited via opportunity sampling and voice-hearer groups.</td>
<td>CVHs had to have persistent AVHs over the last 6 months, HVHs not specified.</td>
<td>CVH: 38.4</td>
<td>CVH: 75.6</td>
<td>- Semi-structured interview covering characteristics of voices, history of voices, triggers, interpretations of voices, coping strategies and traumatic life events</td>
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<td></td>
<td>15 HVH</td>
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<td>HC: 56.0</td>
<td>HC: 73.0</td>
<td>- Dissociative Experience Scale</td>
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<td>- Composite International Diagnostic Interview</td>
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<td>Study</td>
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<td>19. Howes et al., 2013*</td>
<td>16 HVH</td>
<td>HVH: 43.9</td>
<td>As Daalman et al., 2011a</td>
<td>HVH: 43.9</td>
<td>HVH: 68.8</td>
<td>- Peters Delusion Inventory</td>
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<tr>
<td></td>
<td>16 HC</td>
<td>HC: 42.8</td>
<td>Daalman et al., 2011a</td>
<td>HC: 42.8</td>
<td>HC: 62.5</td>
<td>- Psychotic Symptoms Rating Scale</td>
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<td>- Schizotypal Personality Questionnaire</td>
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<td>- Global Assessment of Functioning Scale</td>
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<td>- [18F]-DOPA Positron Emission Tomography</td>
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<td>- Structured Clinical Interview for DSM-IV II</td>
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<td>- Personality Disorders</td>
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<td>- Comprehensive Assessment of Symptoms and History</td>
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<td>Voice-hearers reported at least occasional voices on the Scale for the</td>
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<td>Assessment of Positive Symptoms</td>
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<td>CVH: 41</td>
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<td>HC: 69</td>
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<td>- Autobiographical Memory Task</td>
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<td>- Appraisals of Anomalous Experiences interview</td>
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<td></td>
<td>- Scale for the Assessment of Positive Symptoms</td>
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<tr>
<td>20. Jacobsen et al., submitted</td>
<td>39 CVH</td>
<td>CVhs were recruited from two UK sites; HVHs were recruited as part of the wider UNIQUE study (see Peters et al., 2016).</td>
<td>Voice-hearers reported at least occasional voices on the Scale for the Assessment of Positive Symptoms</td>
<td>CVH: 41</td>
<td>CVH: 36</td>
<td>- WAIS-III</td>
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<td></td>
<td>35 HVH</td>
<td>HVH: 45</td>
<td>Daalman et al., 2011a</td>
<td>HVH: 45</td>
<td>HVH: 74</td>
<td>- BDI-II</td>
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<td></td>
<td>77 HC</td>
<td>HCs: 45</td>
<td>Daalman et al., 2011a</td>
<td>HCs: 45</td>
<td>HCs: 69</td>
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<td>Study</td>
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<td>Group characteristics</td>
<td>AVH Selection</td>
<td>Mean Age</td>
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</table>
| 21. Krakvik et al., 2015 | 30 CVH  140 HVH  2359 HC | Swedish population cohort; 8000 contacted of whom 2533 responded with questionnaire data | Two LSHS items were used: “In the past I have had the experience of hearing a person’s voice and then found that there was no-one there” and “I often hear a voice speaking my thoughts aloud”. Those who answered yes to both items were asked additional questions about voice characteristics. | CVH: 44.3 HVH: 42.2 HCs: 52.1 | CVH: 43.3 HVH: 62.9 HCs: 54.3 | - Launay-Slade Hallucination Scale  
- Hospital Anxiety and Depression Scale  
- Additional questions regarding stressful life events, voice phenomenology and mental health problems |
| 22. Kompus et al., 2013 | 8 CVH  8 HVH  8 HC | HVHs were recruited via opportunity sampling. Individuals with sleep-related hallucinations were excluded, so were those with psychiatric treatment. | HVHs were characterised by either hearing voices when no one is around, or hearing their own thoughts as voices. | CVH: 31.1 HVH: 39.3 HCs: 36.3 | CVH: 62.5- HVH: 62.5 HCs: 87.5 | - Psychotic Symptoms Rating Scale  
- fMRI  
- Consonant-vowel Dichotic Listening Task  
- Hughson-Westlake Audiometric Test |
<table>
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<tr>
<th>Study</th>
<th>Sample</th>
<th>Group characteristics</th>
<th>AVH Selection</th>
<th>Mean Age</th>
<th>% Female</th>
<th>Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>23. Lawrence et al., 2010</td>
<td>184 HVH 71 CVH (external sample)</td>
<td>HVH individuals were only included if they had not sought psychiatric help for their voices, or heard voices when under the influence of substances.</td>
<td>Individuals were included if they reported currently hearing voices or having heard voices in the past.</td>
<td>HVH: 34.5 CVH: -</td>
<td>HVH: 68.5 CVH: -</td>
<td>- Hospital Anxiety and Depression Scale - Beliefs about Voices Questionnaire – Revised - Topography of Voices Rating Scale (3 items only)</td>
</tr>
<tr>
<td>24. Leudar et al., 1997</td>
<td>14 CVH 14 HVH</td>
<td>None of the HVHs were in contact with psychiatric services. Formal screening for psychiatric symptoms was not possible. Most HVHs were occasional cannabis users. CVHs were schizophrenia patients recruited from mental health services.</td>
<td>HVHs reported hearing voices in an on-going survey.</td>
<td>CVH: 31.7 HVH: 22.9</td>
<td>CVH: 35.71 HVH: 57.14</td>
<td>- Structured Interviews</td>
</tr>
<tr>
<td>25. Linden et al., 2011</td>
<td>7 HVH 7 HCs</td>
<td>Participants had no history of psychiatric or neurological illness and were recruited via opportunity sampling.</td>
<td>Recruitment occurred via self-reports, AVHs were assessed with PANSS.</td>
<td>HVH:45.0 HCs: 31.0</td>
<td>HVH: 71.4 HCs: 71.4</td>
<td>- Positive and Negative Syndrome Scale - Beliefs about Voices Questionnaire - BOLD fMRI during AVHs (indicated by button press)</td>
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<tr>
<td>Study</td>
<td>Sample</td>
<td>Group characteristics</td>
<td>AVH Selection</td>
<td>Mean Age</td>
<td>% Female</td>
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<tr>
<td>26. Moritz and Laroi, 2008</td>
<td>46 CVH</td>
<td>Of the CVHs and CNVHs, 45 had schizophrenia, 60 had OCD. Individuals were classified as HCs and HVHs if they denied the presence of any psychiatric illness and contact with any mental health services.</td>
<td>AVHs were assessed as having heard voices when no-one was around.</td>
<td>GP: 35.6</td>
<td>GP: 65.5</td>
<td>- Yale-Brown Obsessive Compulsive Scale</td>
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<tr>
<td></td>
<td>17 HVH</td>
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<td>OCD: 32.7</td>
<td>OCD: 61.7</td>
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<td>69 CNVH</td>
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<td>SZ: 35.9</td>
<td>SZ: 46.7</td>
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<td></td>
<td>38 HC</td>
<td>(partially collapsed samples)</td>
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<td>27. Peters et al., 2016</td>
<td>92 PE</td>
<td>Study recruited healthy individuals with psychotic experiences (PEs), who were assessed as having no need for care and no previous diagnosis for a psychotic disorder.</td>
<td>Voice-hearing was assessed using the Scale for the Assessment of Positive Symptoms. Analysis on voice-hearing was carried out only in relation to Southampton Mindfulness Questionnaire.</td>
<td>PE: 46</td>
<td>PE: 72.8</td>
<td>- Scale for the Assessment of Positive Symptoms</td>
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<td></td>
<td>84 CPE</td>
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<td>CPE: 42</td>
<td>CPE: 34.5</td>
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<td>83 HC</td>
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<td>HC: 46</td>
<td>HC: 68.7</td>
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<td>Study</td>
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<td>Group characteristics</td>
<td>AVH Selection</td>
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| 28. Slotema et al., 2012* | 38 BPD-CVH | As Daalman et al., 2011a | As Daalman et al., 2011a | BPD-CVH: 34.0 | BPD-CVH: 100.0 | - Structured Clinical Interview for DSM-IV II - personality disorders  
- Comprehensive Assessment of Symptoms and History  
- Psychotic Symptoms Rating Scale - Auditory Hallucinations |
| | 51 SZ-CVH | 51 SZ-CVH | 37.0 | SZ-CVH: 100.0 | 100.0 | |
| | 66 HVH | 66 HVH | HVH: 37.0 | HVH: 100.0 | |
| 29. Sommer et al., 2010a* | 103 HVH | As Daalman et al., 2011a | As Daalman et al., 2011a | HVH: 44.0 | HVH: 70.8 | - Comprehensive Assessment of Symptoms and History  
- Psychotic Symptoms Rating Scale - Auditory Hallucinations  
- Launay-Slade Hallucination Scale  
- Global Assessment of Functioning Scale  
- Structured Clinical Interview for DSM-IV II - personality disorders  
- Schizotypal Personality Questionnaire  
- Peters Delusion Inventory  
- Revised NEO Personality Inventory  
- Childhood Trauma Questionnaire |
<p>| | 60 HC | 60 HC | HC: 46.0 | HC: 70.0 | |</p>
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<th>Study</th>
<th>Sample</th>
<th>Group characteristics</th>
<th>AVH Selection</th>
<th>Mean Age</th>
<th>% Female</th>
<th>Measures</th>
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<tbody>
<tr>
<td>30. Sommer et al., 2010b*</td>
<td>40 CVH 40 HVH 50 HC</td>
<td>As Daalman et al., 2011a</td>
<td>As Daalman et al., 2011a</td>
<td>CVH: 40.0 HVH: 41.0 HC: 44.0</td>
<td>CVH: 48.0 HVH: 62.0 HC: 70.0</td>
<td>- Comprehensive Assessment of Symptoms and History</td>
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<td></td>
<td>- Launay-Slade Hallucination Scale</td>
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<td>- Structured Clinical Interview for DSM-IV II - personality disorders</td>
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<td>- Schizotypal Personality Questionnaire</td>
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<td>- Peters Delusion Inventory</td>
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<td>- Thought and Language Index</td>
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<td>- Thematic Apperception Test</td>
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<td></td>
<td>- Global Assessment of Functioning Scale</td>
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<tr>
<td>31. Sorrell et al., 2010</td>
<td>32 CVH 18 HVH</td>
<td>Participants were excluded if they heard voices due to an organic illness or substance misuse. CVHs were recruited from mental health services. HVHs were excluded if they currently had contact with mental health services in relation to voice-hearing.</td>
<td>Individuals heard voices for at least 6 months.</td>
<td>CVH: 38.1 HVH: 54.3</td>
<td>CVH: 41.0 HVH: 67.0</td>
<td>- Psychotic Symptoms Rating Scale</td>
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<td>- Voice and You Questionnaire</td>
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<td>- Beliefs about Voices Questionnaire - Revised</td>
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<td>- Beck-Depression Inventory - II</td>
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<td>32. Taylor and Murray, 2012</td>
<td>6 HVH</td>
<td>Participants were included if they reported no frequent distress and reported no contact with mental health services in relation to their voice experiences. Participants were self-identified mediums.</td>
<td>Self-reported &quot;clairaudience&quot; or hearing the voices of spirits was taken as a proxy for AVHs.</td>
<td>48.5</td>
<td>66.7</td>
<td>- Qualitative Interviews</td>
</tr>
<tr>
<td>33. van Lutterveld et al., 2010*</td>
<td>18 HVH 18 HC</td>
<td>As Daalman et al., 2011a</td>
<td>As Daalman et al., 2011a</td>
<td>HVH: 42.8 HC: 43.8</td>
<td>HVH: 83.3 HC: 83.3</td>
<td>- Comprehensive Assessment of Symptoms and History - Structured Clinical Interview for DSM-IV II - personality disorders - Schizotypal Personality Questionnaire - Peters Delusion Inventory - EEG - auditory oddball paradigm</td>
</tr>
<tr>
<td>34. van Lutterveld et al., 2014*</td>
<td>50 CVH 50 HVH 50 HC</td>
<td>As Daalman et al., 2011</td>
<td>As Daalman et al., 2010</td>
<td>CVH: 39.9 HVH: 40.8 HC: 40.5</td>
<td>CVH: 62.0 HVH: 62.0 HC: 62.0</td>
<td>- Comprehensive Assessment of Symptoms and History - Structured Clinical Interview for DSM-IV II - personality disorders - Positive and Negative Syndrome Scale - Schizotypal Personality Questionnaire - Global Assessment of Functioning Scale - MRI</td>
</tr>
<tr>
<td>Study</td>
<td>Sample</td>
<td>Group characteristics</td>
<td>AVH Selection</td>
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</table>
| 35. Varese et al., 2015 | 18 HVH  
22 CVH | Recruitment sources not clear | HVHs were individuals with no current or past mental health difficulties. CVHs had previously received diagnoses. | CVH: 37.8  
HVHs: 39.9 | CVH: 45.5  
HVH: 38.9 | - Psychotic Symptoms Rating Scale  
- Cognitive Assessment of Voices Interview  
- Modified Goals Task |
| 36. Woods et al., 2015 | 26 HVH  
127 CVH | Online questionnaire; anyone hearing voices was free to participate. Some subgroup analyses were carried out in relation to whether individuals had received mental health care. | Participants were included if they reported hearing voices. | n/a; range 16-84 | 65.4 | - Self-reported qualitative questionnaire comprising 13 items |

Note: CVH – Clinical Voice Hearer; HVH – Healthy Voice Hearers; HC – Healthy Control; Gen Pop – General Population Sample; BPD – Borderline Personality Disorder; SZ – Schizophrenia; CNVH – Clinical participants who do not hear voices; C – Christian; NR – Non-religious; PE – Healthy individuals with psychotic experiences; CPE – Clinical individuals with psychotic experiences; n/a – not available; * - indicates that studies belong to the same Dutch cohort; 1 – no separate means provided.
2.3 Results

2.3.1 Methodology

Out of the 36 studies reviewed, 17 were drawn from the Dutch (Utrecht) sample of HVHs, comparing them to HCs and/or CVHs. These studies employed the same selection and screening criteria, which were amongst the most stringent (see Table 2.2). Although these studies generally had different main outcomes, some of the basic data such as voice phenomenology were assessed in samples recruited from the same cohort, albeit with slightly different participant numbers in each. Therefore, separate publications may report the same finding, confounding any cumulative strength of evidence by the shared participants across studies. Nevertheless, these studies had different clinical and/or healthy control samples, and did not always report the same results on the same measure. Therefore, they are still reported as individual findings, but with an indication (*) that they belong to one cohort (see Table 2.2 & Table 2.3).

Sample sizes differed considerably depending on methodology employed across all 36 studies. As would be expected, studies relying largely on questionnaire-based data had larger sample sizes than studies using neuroimaging or qualitative assessments. Although a priori matching across samples for at least one variable occurred in a sizeable minority of studies, primarily handedness, gender and/or age, several studies reported that samples did not match on education. Moreover, it should be noted that both CVH and HVH within and between individual studies are likely to show considerable degrees of heterogeneity, both due to differences in recruitment strategies and sources, as well as differing diagnoses in CVHs.
2.3.2 Phenomenology

Twenty-seven of the reviewed studies reported on the phenomenology of voices in some capacity, 14 of which were from the same cohort. Phenomenological similarities and differences in AVH are presented in Table 2.3, and summarised below, in a subset of 17 studies that compared the major phenomenological characteristics of AVHs in HVHs and CVHs. Finally, Daalman et al. (2016*) report that AVHs in non-clinical samples show a high level of persistence, with continued experience of AVHs in 86.4% of their sample at 5-year follow-up.
<table>
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<tr>
<th>Study</th>
<th>Duration</th>
<th>Frequency</th>
<th>Loudness</th>
<th>Location</th>
<th>Beliefs of Origin</th>
<th>Number of Voices</th>
<th>Negative Voice Content/Valence</th>
<th>Control</th>
<th>Disruption</th>
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<tr>
<td>3. Andrew et al., 2008</td>
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<td>15. Krakvik et al., 2015</td>
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<td>16. Leudar et al., 1997</td>
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<td>17. Moritz and Laroi, 2008*</td>
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<td>18. Slotema et al., 2012*</td>
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<td>19. Sommer et al., 2010b*</td>
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<td>20. Sorrell et al., 2010</td>
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Note: ↑ indicates greater in HVHs than CVHs, ↓ indicates lower in HVHs than CVHs, = indicates similar in HVHs and CVHs, - indicates no results available; * indicates that studies belong to the same Dutch cohort; † when comparing HVHs to CVHs with a diagnosis of schizophrenia (as opposed to OCD).
### 2.3.2.1 Age of Onset

Five out of six publications comparing age of AVH onset reported an earlier age in HVHs than CVHs (Daalman et al., 2011a*; De Weijer et al., 2013*; Honig et al., 1998; Sorrell, Hayward, and Meddings, 2010), with age of onset in HVHs typically occurring between late childhood and early adolescence (Daalman et al., 2011a*; Linden et al., 2011; Sommer et al., 2010a*; van Lutterveld et al., 2010). However, Kråkvik et al. (2015) did not find a significant difference in age of onset between CVHs and HVHs.

### 2.3.2.2 Frequency and duration of voices

Fourteen out of 15 studies reported a lesser frequency of voice-hearing in HVHs, with only one study failing to find a significant difference. Similarly, eight out of ten studies reported a lesser duration of hallucinatory episodes in HVHs, although two found no difference between HVHs and CVHs.

### 2.3.2.3 Perceptual Qualities

Eleven studies compared the loudness of voices between HVHs and CVHs, with 8 finding no significant difference, two reporting quieter voices and one reporting louder voices in HVHs. Similarly, in 10 studies all but one reported that the perceived location of voices did not differ between HVHs and CVHs, with only one reporting that HVHs were more likely to perceive them as located inside the head (Leudar, Thomas, McNally, and Glinski, 1997). There is some evidence that HVHs perceive their voices with less clarity than CVHs (Cottam et al., 2011; Lawrence, Jones, and Cooper, 2010), but similar rates report their voices as indistinguishable from real voices (Moritz and Larød, 2008).


2.3.2.4 Voice identities

Three out of four studies reported that HVH heard fewer different voices, particularly those commenting in the 3rd person. The majority of HVHs appear to hear one voice, although a sizeable minority hear multiple voices, with more than 10 in 5.4% of HVHs (Lawrence et al., 2010). According to Sommer et al. (2010a*) 18% of HVHs reported commenting voices, and 11% heard voices speaking with each other; similarly, Peters et al. (2016) reported fewer commenting or conversing voices in HVHs compared with CVHs. Leudar and colleagues (1997) reported that both CVHs and HVHs are addressed by voices directly, and voices commonly sound like individuals known to the voice-hearers; whilst voices in the clinical group are more frequently those of public figures or supernatural characters, HVHs are more likely to identify voices as similar to themselves or family members (Leudar et al., 1997). However, Kråkvik et al. (2015) found no differences in the voice identities reported by CVHs and HVHs. Further, Sorrell et al. (2010) reported that gender and identity of AVHs does not appear to differ between groups. Religious groups more frequently identified their voices to be religious entities, however HVHs more often heard “God” and rarely “the Devil”, whilst CVHs more often heard “the Devil” but rarely “God” (Cottam et al., 2011).

2.3.2.5 Content

Of the 14 studies comparing HVHs and CVHs, all reported lower levels of negative voice content and emotional valence in HVHs. Indeed, in one sample 71% of HVHs had never experienced negative voice content (Sommer et al., 2010a*). Similarly, voices in religious HVHs mostly have mixed or neutral content, whereas religious CVHs mostly hear mixed and negative content (Cottam et al., 2011). However, Beavan and Read (2010) found that, in a sample of CVHs and HVHs that were not formally stratified by clinical status, no participants had experienced positive voice content only. In a small qualitative study, Leudar et al. (1997) found that directive voices
in CVHs frequently issued commands to carry out specific actions or violent acts, but in HVHs they more commonly “gave advice” on a particular course of action or mundane activities. HVHs heard significantly fewer negative evaluative comments about themselves, including their own thoughts (Honig et al., 1998), but heard significantly more comments evaluating others. This was also reported in the larger sample of Kråkvik et al. (2015), where HVHs were less likely to hear voices commenting on them. Whilst there was no difference in commanding voices, CVHs were more compliant with and swayed by commands. Interestingly, Varese et al. (2015) identified personal goals (e.g., being a confident person) as a substrate of voice content: in the majority of both CVHs and HVHs, personal goals of participants matched the content of the voices they experienced.

2.3.3 Voice Impact and Appraisal

2.3.3.1 Distress and Control

As would be expected, out of the 23 studies investigating distress all reported that voice-hearing in HVHs was associated with little to no voice-related distress, and/or that voice distress was significantly higher in CVHs. Comparing HVHs and CVHs, 10 studies found that HVHs reported greater control over voices, with only two studies finding the same level of control in HVHs and CVHs. Indeed, one study reported that healthy status was significantly predicted by high control over voices, low frequency of voices, age of onset before age 16, and predominantly positive voice content (Daalman et al., 2011a*). Need for control and low perceived control were also found to predict voice-distress by Hill et al. (2012), while Beavan and Read (2010) reported that negative emotional responses were predicted by negative voice content, more voices talking or arguing with each other, commenting on the individual, talking for longer periods, and taking over thoughts of the individual (Beavan and Read, 2010), as well as disturbing contact with others (Kråkvik et al, 2015). CVHs are significantly more afraid of voices than HVHs, and see voices as troublesome and disturbing daily life (Honig et al., 1998). Interestingly however, one
study indicated that despite negative elicited emotions being more likely to be reported by the
CVH group, there was no significant difference in positive emotions elicited by AVHs in CVHs and
HVHs (Kråkvik et al., 2015). Nonetheless, more than 90% of HVHs report no disturbance to their
life by AVHs (Sommer et al., 2010a*), and all six studies comparing the disruptive impact of
voices between HVHs and CVHs reported less disruption in HVHs.

2.3.3.2 Beliefs about Voices

Out of the eight studies comparing beliefs of origin between HVHs and CVHs, six found that HVHs
were more likely to attribute the voices to external origins, whereas two found no significant
difference between the groups. All of the six studies assessing beliefs about voices indicate that
HVHs have significantly less negative beliefs about voices, which is associated with more positive
voice impact. Hill et al. (2012) reported that CVHs scored higher than HVHs on negative beliefs
about worry and need for control of voices. Voice-related distress was significantly associated
with negative beliefs about uncontrollability and danger of voices. Lawrence et al. (2010) found
that, compared to scores from a previously published sample of CVHs, HVHs had significantly
lower beliefs of malevolence, omnipotence and resistance towards voices, but higher scores of
benevolence and engagement with voices. Levels of distress correlated with malevolence,
omnipotence and resistance. Higher frequency was associated with higher levels of depression,
anxiety, malevolence, omnipotence and resistance. Andrew et al. (2008) found that CVHs were
more likely to appraise their voices as malevolent, which was predictive of depressive
symptoms, and were more likely to use resistant coping strategies. Similarly, Kråkvik et al. (2015)
found that CHVs were more likely to try to actively ignore voices, including command
hallucinations (Leudar et al., 1997), and to try to understand them or argue with them, whilst a
greater proportion of HVHs than CVHs were likely to do nothing in response to AVHs. Further,
CVHs who begged voices to keep silent reported increased AVH intensity (Kråkvik et al., 2015).
In turn, Peters et al. (2016) reported that HVHs were more likely to be accepting of their voices,
and adopt a mindful response style compared with CVHs. Qualitative data suggest that in HVHs, the initial reaction is marked by resistance, which is associated with increased intrusiveness, but eventually engagement (i.e. understanding and acceptance of experience) mitigates distress (Taylor and Murray, 2012). Sorrell et al. (2010) reported that HVHs related to their voices with less distance. Voice dominance, intrusiveness and hearer distance were significantly correlated with distress. However, when controlling for beliefs of malevolence and omnipotence, the association of distress and relating variables lost significance. Recently, Daalman et al. (2016*) provided evidence that attitudes towards AVHs can be susceptible to fluctuations, with beliefs about voices changing in 15.7% of HVHs at a 5-year follow-up.

### 2.3.3.3 Spiritual Frameworks

All four studies reporting on spiritual or religious frameworks showed that these are more frequently employed by HVHs, with generally positive perceived impact. Daalman et al. (2011a*) reported that HVHs more frequently endorsed unspecific external or spiritual explanations, whereas CVHs more frequently explained voices to be other (living) people, god, demons/devil or implanted devices. In their comparison of religious HVHs to religious and non-religious CVHs, Cottam et al. (2011) found that religious HVHs more often experienced AVHs as a positive but never a negative power, whereas most clinical participants (both religious and non-religious) appraised them as a negative power. Similar findings were reported by Davies et al. (2001), with religious HVHs having significantly more positive perceptions of voices than non-religious HVHs and CVHs, respectively. In a qualitative study of HVHs recruited as psychic mediums, initial voice distress was mitigated by engagement with voices and integration into a spiritual framework (Taylor and Murray, 2012).
2.3.4 Mood Disturbances

Three studies formally assessed mood disturbances in HVHs, comparing them to CVHs but not to HCs, with all three finding higher rates of emotional difficulties in the CVHs. Andrew et al. (2008) reported greater rates of depression and anxiety in CVHs compared with HVHs. Similarly, Sorrell et al. (2010) reported significantly greater depression scores in CVHs than HVHs. Lawrence et al. (2010) found that scores for anxiety and depression were significantly lower in HVHs than for 71 CVHs in an external study sample. However, a number of studies (see Table 2.2) stipulated an absence of diagnosable affective disturbances as part of their inclusion criteria for HVHs. Nevertheless, Sommer et al. (2010a*) additionally reported on previous single or recurrent depressive episodes in full remission, and found that HVHs and HCs did not differ in their prevalence. The only study that compared depressive and anxiety symptoms in CVHs, HVHs and HCs reported significant group differences between all groups (Kråkvik et al., 2015) with CVHs having the highest scores and HCs having the lowest scores. Indeed, the HVHs in this sample were also significantly more likely than HCs (but less likely than CVHs) to have consulted a professional or received treatment for mental health problems unrelated to voice-hearing. Woods et al. (2015)’s survey data showed that in voice-hearers who had not previously received a psychiatric diagnosis their voices were less likely to be associated with fear or depression. Most recently, Daalman et al. (2016*) provided 5-year follow-up data on the mental health of their sample of HVHs as well as HCs. Eighty-one individuals with AVHs and 49 HCs were included, representing 78.6% and 81.7%, respectively, of the original participants. Five individuals with AVHs had transitioned to psychosis yet none of the HCs had developed psychosis. This difference was only at trend-level, and disappeared when individuals with previous depressive episodes who were in remission at baseline were excluded. However, they also found that 39.5% of their previously healthy voice-hearers had developed the need for mental healthcare, significantly more than the 12.2% of the healthy control group, even after exclusion of individuals with
depression in remission at baseline. Regression analyses revealed that this need for mental healthcare was predicted by total distress of AVHs and depression in remission, but not global functioning, schizotypy, familial psychosis, childhood trauma, or AVH frequency, control, emotional valence or age of onset.

### 2.3.5 Impairment and Functioning

Seven of the identified studies, all of which stem from the same Dutch cohort, reported on the potential impairment of HVHs, suggesting some impairments in global functioning that may be lesser than those of CVHs, yet greater than in HCs. Sommer et al. (2010a*) found that global functioning was significantly lower in HVHs than HCs, and was predicted by genetic loading (i.e. prevalence of familial psychiatric disorder). This was corroborated by Diederén et al. (2010*) and van Lutterveld et al. (2014*), who found that CVHs, HVHs and HCs all differed significantly from each other in their global functioning, with CVHs scoring the worst, and HVHs scoring better than CVHs yet worse than HCs. Additionally, Diederén et al. (2010*) reported that CVHs showed reduced global functioning compared to HVHs. Howes et al. (2013*) and Diederén et al. (2013*) reported that HVHs showed no impairment in global functioning, but did not compare the results of HVHs to HCs. De Weijer et al. (2013*) reported global functioning scores as part of their demographic variables, showing lower scores in functioning of HVH compared to HCs, but did not report on the statistical significance of this difference. Based on the reported data, we conducted a two-tailed t-test assuming unequal variances for a more conservative estimate, showing that this difference was significant ($p = 0.005, t = 2.95$).

### 2.3.6 Related Psychotic Phenomena

Six studies investigated other psychotic experiences in HVHs. Sommer et al. (2010b*) investigated thought disorder in CVHs, HVHs and HCs using a thought and language index and a thematic apperception test. Impoverishment of language was almost exclusively present in
CVHs. Disorganisation scores were significantly lower in HCs than HVHs and CVHs, but HVHs were significantly less disorganised than CVHs. Additionally, Sommer et al. (2010a*) reported that there was greater preoccupation with, and conviction of, delusional ideation in HVHs than HCs. Hill et al. (2012) found that CVHs scored higher than HVHs on positive symptoms, negative symptoms and symptoms of general psychopathology. HVHs did not differ significantly from HCs on negative symptoms and general psychopathology, but scored higher on positive symptoms, which lost significance when the hallucination item was excluded. Sommer et al. (2010a*) reported greater schizotypy scores in HVHs compared to HCs, with significant elevations on all subscales including non-positive dimensions. Interestingly, schizotypy scores, alongside genetic family loading and number of years of education, predicted global functioning. Higher schizotypy was also observed amongst HVHs compared to HCs in another study (van Lutterveld et al. 2014*), however schizotypy scores in one HVH group were similar to published general population estimates (Howes et al., 2013*). Further, the majority of HVHs experience other hallucinatory experiences, most commonly in visual, olfactory and tactile sensory domains (Sommer et al., 2010a*; Peters et al., 2016).

2.3.7 Cognitive Biases

Two studies investigated the presence of cognitive biases in HVHs. Daalman et al. (2012b*) compared CVHs, HVHs and HCs on cognitive biases for psychosis, including jumping to conclusions (reaching conclusions with limited information), intentionalising (suspecting ill intent in the actions of others), catastrophizing (endorsing the worst possible outcome of a situation), dichotomous thinking (appraising situations in extremes rather than gradients of good and bad) and emotional reasoning (emotion-driven reasoning, such that appraisals are based on internal emotional states). HCs had significantly lower cognitive biases scores than both HVHs and CVHs, and HVHs had lower scores than CVHs. However, there were different patterns depending on which type of bias/vignette content was examined: HCs and HVHs scored
significantly lower than CVHs on intentionalising, catastrophising, dichotomous thinking and jumping to conclusions subscores, and did not differ from each other; while both AVH groups scored significantly higher on the emotional reasoning subscale compared to HCs and did not differ from each other. CVHs scored significantly higher on vignettes with threatening themes than both HCs and HVHs, who did not differ from each other. In contrast, both CVHs and HVHs scored significantly higher on vignettes with themes relating to anomalous perceptions compared with HCs, and did not differ from each other. Emotional (voice-distress and emotional valence) as well as cognitive (beliefs about origin, control and disruption) interpretations of AVHs were significant predictors of cognitive bias scores. Similarly, Jacobsen et al. (Under Review) found evidence for a more overgeneral autobiographical memory bias in CVHs compared to HVHs and HCs. Moreover, voice-specific autobiographical memory was more overgeneral in CVHs than in HVHs.

2.3.8 Cognitive Functioning

A total of five studies, all but one stemming from the Dutch cohort, investigated cognitive functioning in HVHs, suggesting few significant differences compared to HCs. HVHs show more errors in top down semantic expectation when compared to HCs (Daalman et al., 2012a*). Moreover, auditory acuity appears somewhat lower in HVHs than HCs (Kompus et al., 2013). Similarly, some cognitive functions, mainly in the verbal domain, have been demonstrated to be significantly lower in HVHs compared to HCs (Daalman et al., 2011b*). Notably however, cognitive functions of HVHs were still within normal ranges. Interestingly, follow-up analysis by Begemann and colleagues (2015*) suggested that differential verbal inhibition in HVHs vs HCs, as measured by the Stroop paradigm (but no other cognitive measures), is fully explained by childhood trauma. A paced verbal fluency task has shown to be equivalent between HVHs, CVHs and HCs (Diederen et al., 2010*). Further, there were no differences observed at the behavioural
level between HVHs and HCs on a test of effortful attention, as assessed via the oddball paradigm (van Lutterveld et al., 2010*).

2.3.9 Neuroimaging

A total of 9 studies used neuroimaging to investigate HVHs, with methodologies ranging from electroencephalography (EEG), functional magnetic resonance imaging (fMRI), structural MRI, diffusion tensor imaging (DTI) as well as positron emission tomography (PET) (Table 2.4; De Weijer et al., 2013*; Diederen et al., 2013*; Diederen et al., 2010*; Diederen et al., 2012*; Howes et al., 2013*; Kompus et al., 2013; Linden et al., 2011; van Lutterveld et al., 2010*, 2014*). Howes and colleagues (2013*) used PET imaging with [18F]-DOPA to investigate dopamine (DA) synthesis capacity in HVHs and HCs. No significant differences were found in whole striatal DA synthesis capacity or associative, limbic and sensorimotor functional subdivisions. Thus, the dopaminergic dysregulation observed in psychosis (Howes et al., 2012) appears not to be present in HVHs. Similarly, in a verbal fluency paradigm (Diederen et al., 2010*), HVHs and HCs did not differ significantly on language lateralisation. CVHs showed greater activation in the right precentral gyrus and left insula than both HVHs and HCs. CVHs also showed greater activation in the right superior parietal lobule than HCs, who did not differ significantly from HVHs.

However, some neurobiological indices appear more similar in HVHs and CVHs. For instance, BOLD contrast fMRI during AVHs was not able to distinguish HVHs and CVHs (Diederen et al., 2012*). Furthermore, Diederen et al. (2013*) reported that during resting-state, HVHs exhibit aberrant connectivity of frontal, superior temporal and parahippocampal areas compared to HCs. Although no CVH sample was included, the authors point towards similar findings in clinical populations, and hypothesise that such alterations underlie the failure of inner speech to be attributed as self-generated. De Weijer et al. (2013*) used DTI and magnetisation transfer
imaging to compare integrity of white matter tracts in CVHs, HVHs and HCs. For the left arcuate fasiculus, both CVHs and HVHs had higher magnetisation transfer ratios than HCs, further suggesting some alterations in white matter connectivity, whilst only CVHs had higher magnetisation transfer ratios in the right arcuate fasiculus compared to HCs but not HVHs, who did not differ significantly from each other. Fractional anisotropy was significantly lower in left arcuate fasiculus, right cortico-spinal tract and bilateral uncinate fasiculi for CVHs only, suggesting altered connectivity and white matter abnormalities to be largely specific to CVHs.

Van Lutterveld and colleagues (2014*) conducted a structural MRI study, comparing CVHs, HVHs and HCs. There were significant group differences in left paracentral lobule, left pars orbitalis, right fusiform gyrus and right inferior temporal gyrus, with CVH lowest, HVH intermediate and HCs showing highest cortical thickness. Right insula thickness was decreased in both CVHs and HVHs compared to controls. In another study however, EEG measures of the oddball paradigm showed activation patterns consistent with increased effortful attention in HVHs, a finding diametrically opposed of that typically observed in psychosis patients (van Lutterveld et al., 2010*). The authors hypothesise that the oddball paradigm is therefore not associated with AVHs per se. Indeed, most of the studies found no association between the neuroimaging indices and assessed AVH parameters (e.g. frequency or emotional valence). This was the case for cortical thickness (van Lutterveld et al., 2014*), striatal dopamine synthesis (Howes et al., 2013*), lateralisation indices (Diederen et al., 2013*) as well as fractional anisotropy and magnetisation transfer ratios (de Weijer et al., 2013*). Thus, with several of these measures it appears likely that the investigated parameter is not AVH-related, but population-specific.
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<th>Study</th>
<th>Paradigm</th>
<th>Tested association</th>
<th>CVH compared to HC</th>
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<tr>
<td>De Weijer et al., 2013*</td>
<td>Diffusion Tensor Imaging Magnetisation Transfer Imaging</td>
<td>↑ Fractional anisotropy in left arcuate fasiculus, right cortico-spinal tract and bilateral uncinate fasciuli ↑ Magnetisation transfer ratio in left arcuate fasiculus ↑ Magnetisation transfer ratio in right arcuate fasiculus ↑ Radial diffusivity in the right arcuate fasiculus</td>
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<td>Diederen et al., 2010*</td>
<td>BOLD fMRI during verbal fluency task</td>
<td>↑ Lateralisation ↓ Activation in right precentral gyrus and left insula - ↓ Lateralisation ↑ Activation in right precentral gyrus, left insula, and right superior parietal lobule</td>
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<td>Diederen et al., 2012*</td>
<td>BOLD fMRI during AVHs</td>
<td>= Activation in a priori hypothesised regions, comprising bilateral inferior frontal gyri, insula, superior and middle temporal gyri, supramarginal gyrus, precentral and post-central gyri, cerebellum, hippocampus and parahippocampal gyrus, as well as across all grey matter voxels = Lateralisation indices n/a n/a</td>
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<td>Study</td>
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<td>HVH compared to CVH</td>
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| Diederen et al., 2013*       | BOLD fMRI during resting-state                                | n/a                 | ↓ Connectivity of left superior temporal gyrus with right and left superior temporal regions  
↑ Connectivity of left parahippocampal gyrus with left inferior frontal region  
= Connectivity of right superior temporal and bilateral inferior frontal regions  
No negative correlation of right inferior frontal gyrus activity with left temporoparietal region in HVHs | n/a                |
| Howes et al., 2013*          | [18F]-DOPA Positron Emission Tomography                      | n/a                 | = Whole striatal dopamine synthesis capacity as well as in associative, limbic and sensorimotor functional subdivisions | n/a                |
| Kompus et al., 2013          | fMRI during dichotic listening task                           | n/a                 | ↓ Primary auditory cortex activation in response to stimulation                      | n/a                |
| Linden et al., 2011          | BOLD fMRI during AVHs (vs imagined voices in HCs)            | n/a                 | ↑ Activation in bilateral inferior parietal lobules, left middle frontal gyrus, posterior cingulate cortex, left Heschl's gyrus and bilateral calcarine sulci  
↑ Time of onset of activity in supplementary motor area, followed by bilateral inferior frontal gyri and superior temporal sulcus | n/a                |
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<th>Study</th>
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<th>Tested association</th>
<th>CVH compared to HC</th>
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<tr>
<td>van Lutterveld et al., 2010*</td>
<td>EEG during oddball paradigm</td>
<td>n/a</td>
<td>↑ P300 amplitudes, processing negativity amplitudes = P300 latency, processing negativity latency, mismatch negativity amplitude and latency</td>
<td>n/a</td>
</tr>
<tr>
<td>van Lutterveld et al., 2014*</td>
<td>MRI</td>
<td>↑ Cortical thickness in left paracentral lobule, left pars orbitalis, right fusiform gyrus and right inferior temporal gyrus</td>
<td>↓ Cortical thickness in left paracentral lobule, left pars orbitalis, right fusiform gyrus and right inferior temporal gyrus ↓ Right insula thickness</td>
<td>↓ Cortical thickness in left paracentral lobule, left pars orbitalis, right fusiform gyrus and right inferior temporal gyrus ↓ Right insula thickness</td>
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</table>

Note: ↑ indicates an increase, ↓ indicates a decrease, = indicates no difference, n/a indicates that no such comparison was conducted
2.3.10 Trauma Exposure

All of the five studies that assessed trauma in HVHs reported increased rates of trauma exposure similar to those in CVHs. Honig et al. (1998) first found evidence of elevated trauma rates in HVHs: whilst childhood trauma rates were significantly higher in CVHs than HVHs, only 27% of HVHs had no history of childhood abuse. Unlike Honig et al., but in a much larger sample, Daalman et al. (2012b*) found that CVHs and HVHs did not differ significantly from each other in prevalence of childhood sexual, physical or emotional abuse, or physical or emotional neglect, which were all higher than in HCs (Sommer et al., 2010a*). Type of trauma did not predict emotional valence or phenomenology of voices. Similarly, Andrew et al. (2008) found no significant differences in exposure rates to traumatic childhood or adulthood events between CVHs and HVHs, although CVHs had higher rates of childhood sexual abuse. Traumatic events were more closely associated with PTSD symptoms in CVHs than HVHs. Trauma predicted beliefs of high malevolence, low benevolence and high omnipotence of voices, as well as higher levels of anxiety. Kråkvik et al. (2015) found higher rates of lifetime trauma exposure in HVHs compared to HCs, but lower than in CVHs. CVHs and HVHs did not differ in their experience of bullying, although a trend-level effect was observed suggesting higher rates in CVHs, and both groups were significantly higher than HCs. Notably, the age of exposure was not assessed. A significantly larger percentage of CVHs had been in dangerous situations or accidents than HVHs, who in turn had a larger exposure to such events than HCs. Interestingly, HVHs were significantly less likely to identify such stressful life events as related to AVH onset, in contrast to CVHs.

2.3.11 Familial Risk

Three of the identified studies reported on the potential familial risk of HVHs. In Linden et al. (2011), 2 of 7 HVH participants reported a first-degree relative with psychosis. Similarly, van Lutterveld et al. (2014*) reported that HVHs and CVHs had a greater number of first- and second-degree relatives with a psychotic disorder compared to HCs, and they did not differ between
each other. Notably, no group differences in the number of relatives with a manic disorder were observed. Conversely, Sommer et al. (2010a*) reported that relatives of HVHs had significantly higher prevalence rates of depressive disorders, mania and substance use disorders than HCs, with a similar trend for psychosis, suggesting higher rates of mental illness in families of both HVHs and CVHs. Further, such apparent genetic loading was predictive of global functioning.

2.4 Discussion

This systematic review identified a total of 36 studies investigating HVHs, spanning various study designs from small qualitative to large epidemiological studies. The literature includes studies investigating voice phenomenology, their impact and appraisal, mood disturbances, impairment and functioning, related psychotic phenomena, cognitive functioning, neuroimaging, trauma exposure and familial risk. Sampling methodologies vary widely, with HVH sample sizes ranging from six to 183, and variable recruitment of HC and/or CVH control samples. The findings need to be interpreted in the context of a number of limitations in the existing literature, which are elaborated below. Most notably, 17 of the 36 reviewed studies are based on variations of the same cohort, which may skew results according to the sampling methodology of those studies, and may inflate the consistency of some of the findings.

2.4.1 Phenomenology and Impact

Contrary to what would be predicted by diagnostic models, the phenomenology of AVHs is overall similar in HVH and CVHs, particularly in form (e.g. loudness or location), but less so in content and incidence (i.e., frequency and duration). However, the selection of samples based on minimum frequency scores of AVHs may lead to a distortion of the phenomenology of AVHs. Wider populations, where AVHs may be distributed with lower frequency, are excluded in most studies. Thus, it cannot be ruled out that parameters such as AVH loudness are actually attenuated once frequency decreases. Large epidemiological research focused on AVHs is
necessary to describe such patterns more accurately, with study designs such as those employed by Woods et al. (2015) and Kråkvik et al. (2015).

The impact and appraisal of AVHs differ substantially between HVHs and CVHs, as would be predicted by a fully-dimensional model where AVHs themselves are insufficient to cause distress. Negative beliefs about voices, such as attributed malevolence and omnipotence, were often predictive of mood disturbances and negative emotional reactivity, as hypothesised by cognitive models of voices (Chadwick and Birchwood, 1994). CVHs consistently report diminished control over their voices, with diminished control as well as need for control being predictive of voice-distress. Although it is likely that the distress of clinical voice-hearers is driven by increased frequencies and negative voice content, a role of ‘top-down processes’ in driving phenomenological characteristics cannot be ruled out. For instance, resistant relationships with voices, a coping style predominantly employed by CVHs, may partially account for the increased frequencies and duration of AVHs in CVHs. HVHs reported that resistance led to initial distress, which was mitigated by engagement (i.e. acceptance and understanding) (Taylor and Murray, 2012). Indeed, HVHs are more likely to have a mindful response style to voices (Peters et al., 2016). This is reminiscent of the thought suppression literature, where it has been found that actively trying to suppress thoughts paradoxically increases their repetitiveness and intrusiveness (Wenzlaff and Wegner, 2000). Thus, it should not be ruled out that phenomenology of voices is shaped by their interactions with ‘top-down’ processes such as appraisals and coping strategies. Similarly, the negative content of voices may be shaped by the presence of mood difficulties, distress or low self-esteem in CVHs, as suggested by the evidence on mood-congruent AVHs (Larøi et al., 2012). In turn, the well-replicated finding that AVH onset occurs significantly earlier in HVHs may explain divergent cognitive appraisals. It could be speculated that earlier onset can be protective against negative appraisals such as thinking that one is “crazy”, as societal stigmatising implications of AVHs may not be understood at that age. However, in the absence of consistent epidemiological and longitudinal evidence, the cross-
sectional evidence reported in the literature makes it difficult to determine the direction of relationships amongst AVHs variables and outcomes.

### 2.4.2 Mental Health and Functioning

Greater rates of depression and anxiety are reported in CVHs compared to HVHs. The relative lack of mood disorders in HVHs again does not support a diagnostic or quasi-dimensional framework, i.e. persistent AVHs can occur independent of distress and mood disturbances. However, these findings need to be viewed in the context of sample selection and stratification in most studies, most notably those of the Utrecht cohort (see Table 2.2) which applied very strict eligibility criteria (i.e., exclusion of any current psychiatric disorder or substance use). Indeed, Kråkvik et al. (2015), using a more open, epidemiological design, did find higher rates of mental health problems in HVHs compared to HCs. Daalman et al. (2016*) further showed that despite good mental health at baseline, their HVHs were at higher risk of developing a need for mental healthcare, most strongly predicted by voice distress and previous mood disturbances. Most of the studies investigating global functioning also showed increased levels of impairments in HVHs compared with HCs, although these tended to be of subclinical magnitude and situated on a continuum between HCs and CVHs. The reviewed studies thus suggest that although HVHs mostly do not require care and suffer no distress (a finding in line with the fully-dimensional model); there is nonetheless some evidence of an increased risk of need for care from epidemiological or longitudinal research (a finding in line with the quasi-dimensional model). Similarly, HVHs score higher than HCs, but lower than CVHs, on disorganisation of thought, show higher levels of delusional ideation than HCs, and have more implicit cognitive biases than HCs, but less than CVHs. Interpreted from a multidimensional standpoint, this may imply that mood disorder and distress are only weakly associated with AVHs, which in turn are more consistently associated with other positive symptoms and cognitive biases. However, since much of the evidence is cross-sectional, it is as of yet impossible to disentangle causal pathways.
The strictly dichotomous stratification in the majority of studies means that clinical individuals who are in remission, or generally healthy individuals who show occasional, subclinical distress, are often excluded in research. Given that the present literature was born out of a reconceptualisation of psychosis towards dimensional models, it is paradoxical that the grey zone in which transitions to and from care-necessitating disturbances occur remains largely unexplored. Differing psychological factors in HVHs and CVHs such as cognitive biases or voice appraisals can, and already do, inform cognitive-behavioural interventions. Therefore, cross-sectional as well as longitudinal research of such transitioning populations, such as that carried out in the literature on at-risk populations, may be most relevant to clinical care and should be addressed in future research.

2.4.3 Risk Factors

HVHs consistently report the presence of well-established latent risk factors for psychosis, i.e. genetic loading (Howes and Murray, 2014) and childhood trauma (Varese et al., 2012). Whilst a greater degree of risk exposure would be expected for both groups in Models 2&3, it is striking that HVHs and CVHs show almost no difference in exposure to these specific risk factors. However, whilst familial incidence of psychiatric disturbances is a reasonable indicator of genetic risk, heritability estimates of AVHs in CVHs and HVHs, as well as molecular genetic and epigenetic investigations, are needed for a more comprehensive understanding. Additionally, a strong case is made for the role of childhood trauma, which was consistently elevated in HVHs across all studies, a finding in line with the highly predictive impact of childhood trauma in the emergence of AVHs demonstrated in other studies (Read, van Os, Morrison, and Ross, 2005; Shevlin, Houston, Dora, and Adamson, 2008). This high rate of trauma exposure in HVHs may also explain the greater risk for distress in HVHs compared to non-voice-hearing members of the general population. Future research should address whether trauma exposure underlies the association of AVHs and distress in the general population.
However, variables such as socioeconomic status or positive social relationships, which may act as further risk or protective factors, have remained unexplored in this context despite their potential relevance. Indeed, in the context of wider psychotic experiences, Peters et al. (2016) showed that non-clinical individuals were less likely to be members of a minority ethnic group, come from a working-class background, live in areas with civic disorder, and were more likely to be employed, have higher educational achievements, and have meaningful relationships. Future research should further investigate adulthood exposure to adversity, stressful life events and everyday stress to assess whether CVHs have greater exposure to the “third hit” proposed in 3-hit models of stress vulnerability (Daskalakis et al., 2013). That is, if HVHs and CVHs largely share the first hit, i.e., a genetic susceptibility, and the second hit, i.e., exposure to childhood traumatic events, then a third hit, i.e., in the form of adversity exposure in early adulthood, may crucially shape the clinical trajectory. The age of exposure to trauma is of great importance for such an assessment and has been omitted in all of the identified studies. Of note, it is surprising that the role of drug use as a risk factor has not been assessed in the literature, potentially due to stringent sampling procedures. However, evidence by Peters et al. (2016) suggests that non-clinical individuals who report wider psychotic experiences are less likely to use drugs than both their clinical counterparts and HCs, a finding that needs replication specifically in the context of HVHs.

### 2.4.4 Neurobiology

Several neuro-cognitive and biological variables appear inconclusive regarding the three frameworks, at least in some domains. Whilst findings on cortical thickness (van Lutterveld et al., 2014*) and white-matter integrity (de Weijer et al., 2013*) are broadly in line with quasi- and fully-dimensional models, several of the functional paradigms showed incongruences with such models. Notably, language lateralisation does not differ between HVHs and HCs, but differs from CVHs (Diederen et al., 2013*, 2010*). EEG-measured response to the auditory oddball paradigm in HVHs diverges from HC populations indicating increased effortful attention,
directionally opposing the well-replicated finding that psychosis is associated with decreased effortful attention (van Lutterveld et al., 2010*). The authors suggest that this primarily indicates that AVHs are unrelated to effortful attention, as correlations of reduced P300 amplitudes with positive or negative symptoms in schizophrenia patients have not been consistently replicated. Notably, this issue translates to several of the investigated variables: it is often difficult to disentangle whether a particular finding is a substrate of AVHs, or a byproduct of wider symptomatology and population differences. Thus, for many of these findings it is not clear whether apparent discontinuity is ultimately one of the phenomenon or the population.

Interestingly, Howes et al. (2013*) reported no differences in DA synthesis capacity between HVHs and HCs. Increased striatal DA synthesis capacity has been a consistent finding in psychosis patients (Fusar-Poli and Meyer-Lindenberg, 2013; Howes et al., 2012) and has also been reported in at-risk individuals (Howes et al., 2011). According to the DA hypothesis (Howes and Kapur, 2009), increased striatal DA signaling leads to aberrant salience attribution to unwarranted stimuli and their associations. Whilst this is hypothesised to lead to the formation of delusional explanations, it is not established whether DA dysregulation actually underlies hallucinatory experiences. The authors (Howes et al., 2013*) conclude that their findings suggest that, at least in the case of non-clinical AVHs, this is not likely to be the case. Speculatively, dysregulated DA synthesis may act as a moderating factor upon which the formation of delusional beliefs secondary to AVHs is contingent, such as threatening appraisals. However, when variables directly associated with AVHs are considered, CVHs and HVHs appear highly similar; for instance, Diederen et al. (2012*) found no differences between CVHs and HVHs in brain activity during acute AVHs, suggesting a shared neurobiological mechanism underlying AVHs in both groups.
2.4.5 Conclusions

The evidence considered in the present systematic review does not support strictly categorical or disease models of psychotic experiences, and is generally inconsistent with a diagnostic conceptualisation (Model 1), thus supporting the first hypothesis. Instead, the evidence supports fully-dimensional and quasi-dimensional models (Models 2 and 3) to a similar degree, and cannot distinguish between them, as predicted by the second hypothesis. Therefore, a hybrid conceptualisation is likely to be the most accurate model (Linscott and van Os, 2013; van Os and Reininghaus, 2016). Characteristics of individual symptoms (e.g. frequency, loudness or content of AVHs) may differ in their continuity between populations, and may feasibly present with skewed or bimodal rather than normal distributions. Especially in the case of bimodal distribution, the contrast between continuous and categorical is left as a primarily semantic issue, as even the most categorical distinctions (e.g. gender) have blurry boundaries (e.g. hermaphroditism or non-binary gender identities). Thus, whilst the evidence ultimately suggests continuity, it is upon future epidemiological research to tease out the complexities and relationships of symptom dimensions. Nonetheless, research on AVHs in healthy populations may prove of crucial value to the understanding and treatment of AVHs in clinical populations.
Chapter 3 – Stress-Function and Psychosis

3.1 Stress-Physiology and Adaptation

3.1.1 Stress, Stress-Reactivity and Allostasis

The term “stress” was first employed in life sciences in the 1930s by early stress researchers such as Hans Selye (Selye, 1936), borrowing it from the field of physics where stress describes the force applied to an object. Although a universal definition of this widely used term remains elusive, it is frequently used to describe pressure, exhaustion or tension, be it psychosocial or biological, that is exerted on an organism and threatens homeostasis (Goldstein and Kopin, 2008; Sapolsky, 2002; Ulrich-Lai and Herman, 2009). The resulting stress reaction can be conceptualised as an acute and/or chronic psychological and physiological state that aims to maintain homeostasis (McEwen, 2000; Sapolsky, 2002). Notably, this threat to homeostasis may be actual or merely perceived, and the stress response can be elicited both in reaction to or anticipation of a stressor (Sapolsky, 2002). As would be expected from terminology that can be applied to both running after a bus and running away from a lion, a definition of such breadth and ambiguity may ultimately have limited power. Thus, the magnitude, duration and context of the stressor and of the stress response are crucial in shaping impact and outcome. Indeed, there is considerable evidence that the magnitude and composition of the stress response varies considerably depending on the specific stressor and the type of threat it poses (Goldstein and Kopin, 2008; Miller, Chen, and Zhou, 2007).

Although often portrayed negatively, the stress response evolved as a highly adaptive process to increase the likelihood of an organism’s survival when exposed to threat (McEwen, 2000). Through adaptive redistribution of physiological and psychological resources towards the purpose of short-term expenditure, the likelihood of survival is optimised, albeit at the cost of temporarily compromising long-term bodily processes such as digestion. The purpose of this shift is perhaps most aptly described by Robert Sapolsky (2004), pointing out that “if there is a
tornado bearing down on the house, this isn’t the day to repaint the garage” (p. 11).

Physiologically, the stress response is marked by activation of two closely related systems, the sympathetic component (SNS) of the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis, both of which release hormones, adrenaline and cortisol respectively, from the adrenal glands (Sapolsky, 2002; Ulrich-Lai and Herman, 2009). In combination, they mount an effort to uphold homeostasis by optimising resource distribution in the body, and inducing the behavioural fight or flight response (Sapolsky, 2002; Ulrich-Lai and Herman, 2009).

Despite this clear evolutionary purpose, the capacity of human beings to engage these stress systems has been recognised to be potentially maladaptive in purely psychosocial contexts, where increased blood flow and energy delivery to skeletal muscles confers virtually no advantage (Sapolsky, 2002). This is the case for both anticipation of and reaction to stressors, particularly so if the stressor is ambiguous. Whilst being attacked by a lion will inevitably lead to a stress response, the stress response to, for instance, unpleasant social situations, is neither inevitable nor helpful (Sapolsky, 2002). Moreover, in the context of chronic employment of psychogenic stress responses, adaptations may occur that impair the future ability to identify and respond to potential stressors adequately.

The term allostasis refers to a process whereby the function of systems such as the ANS and HPA axis is chronically altered to maintain homeostatic processes (Danese and McEwen, 2012; McEwen, 2008). States of chronic hyper- or hypo-activation of these systems have been identified in the aetiology and maintenance of several psychological and biomedical pathologies (Baumeister et al., 2014; Danese and McEwen, 2012; McEwen, 2008). These maladaptive states are typically described as allostatic load, and are associated with altered stress profiles. An appropriate stress response requires a marked activation of stress systems, as well as a rapid deactivation with cessation of the stressful stimulus. Sluggish or hypervigilant onset or recovery, as well as attenuated or augmented peak response, are indicators of excessive allostatic load.
(McEwen, 2000, 2008). Similarly, basal function of those systems may be augmented or attenuated. Maladaptive changes may develop through exposure to chronic or traumatic stressors, to which there is particular vulnerability in early developmental stages but which may also occur later in life (Danese and McEwen, 2012). Indeed, it has been proposed that pathophysiological changes arise through a three hit model: the first hit being genetic predisposition or dispositional susceptibility, the second being exposure to stressful experiences in childhood, and the last being exposure in later life (Daskalakis et al., 2013).

3.1.2 The Autonomic Nervous System

The most immediate physiological stress reaction is mediated by the SNS, which is one of the three branches of the ANS. The other two branches are the enteric and the parasympathetic nervous system (PNS), which control digestion as well as processes diametrically opposed to those of the sympathetic nervous system, respectively (Sapolsky, 2002). SNS activity is induced in response to homeostatic disturbances, such as blood loss, pain or inflammation, and several structures of the brain stem and spinal cord, including the medulla and preganglionic neurons, are activated almost instantaneously (Goldstein and Kopin, 2008; Ulrich-Lai and Herman, 2009). The neurotransmitter noradrenaline is released from the locus coeruleus in the CNS as well as sympathetic nerves, and the sympa-tho-adrenal-medullary (SAM) axis is activated, causing release of the hormone adrenaline from the adrenal medulla, the inner section of the adrenal glands.

Noradrenaline and adrenaline induce tachycardia, vasoconstriction, bronchodilation, hyperventilation and hypertension, in order to optimise blood and oxygen delivery to the brain as well as skeletal muscle (Goldstein and Kopin, 2008; Sapolsky, 2002). Moreover, the SNS stimulates energy mobilisation through the stimulation of glycogen and fat metabolism to increase glucose and free fatty acids in blood (Sapolsky, 2002). They further stimulate activity of the inflammatory immune system to pre-empt injury and subsequent infection (Sapolsky, 2002).
Finally, high levels of SNS activity can induce the fight-or-flight response, a state marked by cognitive and behavioural hypervigilance, increased arousal as well as anxiety and irritability (Morilak et al., 2005; Sapolsky, 2002; Ulrich-Lai and Herman, 2009). Interestingly, the noradrenergic response has a lower threshold and responds to events such as orthostasis, locomotion, mild blood loss and cold exposure, whereas adrenergic responses are only initiated in situations that pose a more substantial threat, such as hypoglycaemia, exercise beyond anaerobic threshold, asphyxiation and considerable blood loss (Goldstein and Kopin, 2008). Thus, some SNS activity also plays a role during situations that do not pose an actual threat to homeostasis and its activity does not necessarily constitute a stress response. The SAM only becomes active once a global threat is established, and indeed there is some evidence that SAM activity may be more closely associated with HPA activity (Goldstein and Kopin, 2008). However, both SNS and SAM adrenal responses appear sensitive to psychological distress (Goldstein and Kopin, 2008). Following stress exposure, there is also a protracted rise in PNS activity, mediated by the nucleus ambiguous and parts of the vagus nerve, to allow the organism to return to homeostasis and resume vegetative function.

### 3.1.3 The Hypothalamic-Pituitary-Adrenal axis

The HPA axis is an endocrine system that is active both in the central nervous system as well as in the periphery, which, like the SNS, is stimulated by the brainstem in response to homeostatic perturbations. Its activity is primarily mediated by secretion of adrenal steroid hormones called glucocorticoids, prominently cortisol in humans (McEwen, 2008; Sapolsky, 2002). It is responsive to acute stimulation through stress exposure, particularly stressors of a psychological nature (Dickerson and Kemeny, 2004), but also follows a diurnal pattern corresponding to periods of rest and activity (Spiga, Walker, Terry, and Lightman, 2014), and shows a rapid oscillatory activity hypothesised to allow for optimal responsiveness (Lightman and Conway-Campbell, 2010). The diurnal slope is described by peak activity in the morning, referred to as the cortisol awakening response, and a trough towards the evening (Spiga et al., 2014). Activation of HPA axis follows
a cascade from the CNS to the adrenal cortices (Sapolsky, 2002; Ulrich-Lai and Herman, 2009).

First, the hypothalamus releases several hormones that can cause down-stream activation of the pituitary gland, including corticotrophin-releasing hormone (CRH), arginine vasopressin (AVP), oxytocin, noradrenaline and adrenaline. Notably, hypothalamic hormone release during stress is idiosyncratic based on particular stress signatures, e.g. whether the organism experiences hypotension or hypoglycaemia, with different orchestrations of hormones triggering the down-stream signalling cascades (Joëls and Baram, 2009; Sapolsky, 2002). These hormones, most prominently CRH, stimulate the pituitary gland to secrete adrenocorticotrophic hormone (ACTH) into circulation, which causes the release of cortisol from the adrenal cortices cranial to the kidneys. Depending on hypothalamic hormone orchestrations, the secretory pattern of ACTH is adapted to a particular stressor (Joëls and Baram, 2009; Sapolsky, 2002).

Following release of cortisol, it is registered throughout the body by its two cognate receptors, the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). These receptors can be found intracellularly within the cytoplasm, but also as membrane receptors. MRs have an up to 10-fold higher affinity for glucocorticoids, and tend to be occupied and activated tonically throughout the day (De Kloet, Vreugdenhil, Oitzl, and Joëls, 1998). During peak HPA activity, e.g. during an acute exposure to a stressful stimulus, glucocorticoid release rises so that following satiation of MRs a higher number of GRs become activated (De Kloet et al., 1998). Once activated, cytoplasmic GRs discard chaperone proteins that bind them, such as the heat-shock protein FKBP5, form palindromic homodimers and translocate to the nucleus (Savory et al., 2001; Silverman et al., 2012). They can then engage in direct protein-protein interactions, e.g., with transcription factors such as the inflammatory messenger NF-kB, but also with glucocorticoid-response elements within the DNA (Zunszain, Anacker, Cattaneo, Carvalho, and Pariante, 2011). In the periphery, this leads to inhibition of the immune system, attenuated release of growth and reproductive hormones including gonadotropin and thyrotropin, and it induces resistance to these hormones as well as insulin in target tissues (Sapolsky, 2002). In the paraventricular nucleus of the hypothalamus and the anterior pituitary gland, activation of the
GR directly induces negative feedback that inhibits the release of CRF and ACTH (Smith and Vale, 2006). Further indirect negative feedback is provided through receptors in limbic, thalamic and frontal regions, which send inhibitory projections to the hypothalamus (Ulrich-Lai and Herman, 2009). It is generally assumed that negative feedback within the HPA axis is primarily mediated by the GR, although some research has also demonstrated fast feedback inhibition through the MR (Atkinson et al., 2008).

3.1.4 The Orchestration of Stress in the Brain

The response to and processing of stress in the brain is highly complex, and in consideration of this the present discussion should not be considered comprehensive, but as highlighting guiding principles. Activity of the two stress systems is initiated by the paraventricular nucleus (PVN) of the hypothalamus, which amongst other hormones releases corticotrophin-releasing hormone (CRH) to stimulate the HPA axis, as well as the locus coeruleus, the primary source of noradrenaline in the brain (Ulrich-Lai and Herman, 2009). Several surrounding regions send afferent nerves to the PVN of the hypothalamus, including the amygdala, the hippocampus, the medial prefrontal cortex, the locus coeruleus as well as the brain stem. These connections are often indirect and relayed through the bed nucleus in the stria terminalis and wider hypothalamus (Smith and Vale, 2006; Ulrich-Lai and Herman, 2009). Further, whilst all of these regions try to influence PVN activity directly, they also branch towards competing regions to inhibit their influence over the PVN (Smith and Vale, 2006; Ulrich-Lai and Herman, 2009). Several higher order systems send associational information to these brain areas, including areas related to sensory processing, such as olfactory nuclei or the thalamus; arousal, such as the locus coeruleus; and memory, such as the entorhinal section of the hippocampus (Smith and Vale, 2006; Ulrich-Lai and Herman, 2009).

Much research has focused on the role of the amygdala, a complex structure of nuclei involved in autonomic regulation and fear responses. Notably, the central nucleus of the amygdala only
shows a response to homeostatic threats, but not to those of a psychogenic nature, whereas the medial and basolateral nuclei do (McIntyre, Kent, Hayley, Merali, and Anisman, 1999; Rajbhandari, Baldo, and Bakshi, 2015). Although the amygdala has no direct projections to the PVN, it can initiate the stress response through γ-aminobutyric-acid (GABA) or glutamatergic projections to other areas such as the bed nucleus of the stria terminalis or the dorsomedial hypothalamus (Ulrich-Lai and Herman, 2009). Animal models have shown substantial amygdaloid remodelling in response to chronic stress exposure, with enhanced dendritic arborisation in the basolateral amygdala (Vyas, Mitra, Shankaranarayana Rao, and Chattarji, 2002). Additionally, prefrontal areas differentially alter the stress response, with prelimbic areas having inhibitory effects, but infralimbic areas showing stimulatory effects on the stress response in the context of psychogenic stressors (Smith and Vale, 2006; Ulrich-Lai and Herman, 2009). Functionally, this means that beyond the impact of physiological stressors such as homeostatic imbalances, pain or inflammation, the stress response is also shaped by top-down processes dependent on cognitive appraisal as well as the integration of memory and experiential factors. As such, the stress response can arise from psychogenic activation, dependent on the competitive activation of key structures in the limbic area.

3.1.5 Effects of Adversity on Physiological Stress-Function

An overwhelming conclusion that has emerged from the literature on stress is that exposure to chronic, inescapable and/or traumatic stress alters stress-function for the worse. Chronic adaptations in activation or attenuation of the stress systems, commonly termed allostatic load (Danese and McEwen, 2012; Korte, Koolhaas, Wingfield, and McEwen, 2005; McEwen, 2000), are detrimental to physical as well as psychological well-being. Allostatic changes in HPA function have been implicated in a number of mental disorders including depressive and anxiety disorders, post-traumatic stress disorder, bipolar disorder and psychosis (Baumeister, Lightman, et al., 2014) and are detrimental to the integrity of the central nervous system (Herbert et al., 2006; McEwen, 2000; McEwen and Gianaros, 2011). Similarly, chronic and excessive activation
of the SNS is associated with allostatic load, including detrimental changes to cardiovascular function such as atherosclerosis (McEwen, 2008). However, although allostasis has been associated with a variety of physical and mental disorders, such dysregulation is specific rather than diffuse. Allostatic changes differ depending on the clinical status of samples, since different psychopathologies have been associated with different, often opposing HPA profiles (Baumeister et al., 2014). For example, total diurnal cortisol output appears elevated in depression (Pariante and Lightman, 2008), yet diminished in post-traumatic stress disorder (Sherin and Nemeroff, 2011). Similarly, negative feedback function within the HPA axis, as measured by cortisol response to the GR-agonist dexamethasone, is blunted in depression (Anacker, Zunszain, Carvalho, and Pariante, 2011) yet hyper-responsive in PTSD (de Kloet et al., 2006).

The experience of early life stress exposure appears to be of crucial importance to such allostatic changes, which have received particular attention in HPA axis research. Healthy individuals with a history of sexual or physical abuse exhibit attenuated HPA activity in adulthood when exposed to psychosocial stress (Carpenter et al., 2007; Carpenter, Shattuck, Tyrka, Geracioti, and Price, 2011; Voellmin et al., 2015). Similarly, GR resistance appears to be altered in individuals with early life trauma (Heim, Mletzko, Purselle, Musselman, and Nemeroff, 2008), and alterations to the cortisol awakening response have also been reported (Lu et al., 2013; Mangold, Wand, Javors, and Mintz, 2010). Interestingly, Carpenter et al. (2009) found that when major depression patients were matched to healthy controls based on childhood adversity as well as on age and gender, dexamethasone-based assessment of GR-function failed to distinguish clinical from non-clinical participants, demonstrating the far-reaching effects of childhood trauma. A key mechanism for such allostatic changes may be epigenetic programming. McGowan et al. (2009) compared GR methylation in hippocampal regions of suicide completers with and without a history of childhood abuse. Greater GR methylation was found in those individuals who had been subjected to early life stress. Similarly, greater methylation of the promoter region of the GR in leukocyte DNA has been found in healthy adults with a history of
childhood stressful experiences (Tyrka, Price, Marsit, Walters, and Carpenter, 2012). These changes were further found to have functional implications, with an attenuated response to the dexamethasone/CRH test. Further, Klengel et al. (2013) found that childhood trauma is associated with demethylation of glucocorticoid response element of the gene coding for FKBP5, a heat shock protein that inhibits the ability of cortisol to bind to cytosolic GR, thus decreasing GR-responsiveness. There is further evidence that childhood trauma impacts on inflammatory immunity, a system in close bidirectional interaction with the HPA axis (Baumeister, Akhtar, Ciufolini, Pariante, and Mondelli, 2015). Thus, early life stress may induce long-lasting changes to functioning of the allostatic systems, even in the context of good mental health in adulthood.

Idiosyncratic types of stress exposure later in life may also impact differentially on HPA signatures. Exposure to episodic stressors in the context of high chronic stress is associated with increased cortisol release and lower GR expression, but exposure to episodic stressors in the context of low chronic stress appears to lead to decreased cortisol release and increased GR expression (Marin, Martin, Blackwell, Stetler, and Miller, 2007). The particular type of threat a stressor poses, for instance to physical integrity or to the social self, is also associated with idiosyncratic HPA profiles (Miller et al., 2007). Moreover, cognitive appraisal of the stressor is crucial in the emergence of the stress response. Anticipatory stress appraisals predict cortisol reactivity to psychosocial stress, as well as sluggish cortisol and blood pressure recovery from the stressor following its cessation (Juster, Perna, Marin, Sindi, and Lupien, 2012). Additional variables related to lifestyle and physical health, such as age (Ferrari et al., 2001), sleep quality (Balbo, Leproult, and van Cauter, 2010), substance use (Schumann, 2006) or metabolic health (Bose, Oliván, and LaFerrère, 2009), may further impact on biological stress-function and lead to allostatic changes that then impair an organism’s ability to adequately respond to stress. Many physical health parameters related to stress-function are further adversely affected, including cardiovascular health, immune-function, metabolic health, growth and tissue repair, sexual function, sleep regulation as well as resilience to energetic crises such as stroke (Juster, McEwen, and Lupien, 2010; Korte et al., 2005; McEwen, 2008).
3.2 Stress-Function in Psychosis

3.2.1 Stress Exposure and Stress-Reactivity in Psychosis

The diathesis-stress model (Nuechterlein and Dawson, 1984; Walker and Diforio, 1997) has long suggested that the interaction of vulnerability factors with exposure to stressors may precipitate onset of psychotic symptoms and disorders, and contribute to their maintenance. A recent variant of the diathesis-stress model, the three hit model of stress exposure (Daskalakis et al., 2013), proposes that any pathology arises through the interplay of 1) genetic, epigenetic or prenatal diatheses, 2) early stressful life events and 3) risk exposure later in life. Indeed, there is substantial evidence to suggest that psychosis patients experience greater exposure to stressful life events. A recent meta-analysis encompassing 18 case-control studies, 10 prospective studies and 8 population-based studies, demonstrated a strong association between exposure to childhood adversity and psychosis (Varese et al., 2012). Psychosis patients were 2.7 times more likely to have experienced childhood adversities than healthy controls, and in population-based studies childhood trauma conferred psychosis risk with an odds ratio of 3.0. Childhood sexual and physical abuse are highly prevalent in psychosis patients, and there is evidence to suggest that such experiences are particularly linked to auditory verbal hallucinations and other positive symptoms (Bentall et al., 2012; Hardy et al., 2016; Read et al., 2005; Shevlin, Dorahy, and Adamson, 2007). Indeed, the relationship with auditory verbal hallucinations appears transdiagnostic, with bipolar disorder patient with childhood trauma exposure experiencing significantly higher rates of voice-hearing than their non-exposed counterparts (Hammersley et al., 2003). Recent evidence further suggests that childhood trauma increases the likelihood of emergence of delusional ideation in the context of hallucinations (Smeets et al., 2015). Interestingly, there is evidence from a prospective general population cohort that the effect of childhood trauma on the distress associated with psychotic experiences is mediated by emotion regulation, although additional analyses revealed that this effect was only significant for paranoid ideation, not hallucinations (Lincoln and Jaya, 2016).
Frequently, the content of positive symptoms is related to the abuse, and there is evidence for a dose-effect relationship between abuse severity and psychosis risk, as well as symptom severity (Read et al., 2005). Evidence from populations at high-risk of developing a psychotic disorder (i.e., individuals with subclinical psychosis symptoms or a high familial risk), suggests higher rates of stressful life events including childhood and adulthood exposure, in such individuals (Bechdolf et al., 2010; Tessner, Mittal, and Walker, 2011; Thompson et al., 2009), although the evidence is not unequivocal (Phillips, Edwards, McMurray, and Francey, 2012). In particular, childhood sexual abuse is associated with an increased risk of transitioning to psychosis in such individuals (Bechdolf et al., 2010). Moreover, stressful life events in adulthood are associated with risk of relapse in psychosis patients (Bebbington et al., 2004; Hultman, Wieselgren, and Ohman, 1997; Malla, Cortese, Shaw, and Ginsberg, 1990). Interestingly, recent evidence suggests that the HPA axis is involved in mediating the risk of trauma exposure on psychosis, with an interaction effect of FKBP5 polymorphisms and childhood trauma on psychotic symptoms and HPA function (Collip et al., 2013a).

As pointed out by Phillips and colleagues (2007), there is a need to move beyond assessment of stressful life experiences when investigating the stress-psychosis relationship, and consider non-traumatic daily stressors (i.e., ‘hassles’) as well as appraisals of potentially stressful situations. Indeed, some studies have reported lower rates of both stressful life events in ultra high-risk and recent-onset psychosis patients longitudinally, yet they appraised life events as more stressful (Horan et al., 2005; Phillips et al., 2012). Several studies have utilised the Experience Sampling Method (ESM), whereby a portable device is used to assess self-reported perceived stress at random times throughout the day. Myin-Germeys et al. (2001) used ESM in psychosis patients in remission, first-degree relatives and healthy controls to assess the stressful impact of events, activities, thoughts and social situations in daily life. Clinical participants were more likely to appraise events in daily life and social situations as stressful compared to healthy controls and first-degree relatives and healthy controls, respectively. Moreover, clinical participants reported significantly more negative affect and less positive affect than the other
two groups. Similarly, individuals at high-risk of developing psychosis are more likely to report daily stressors as more distressing (Phillips et al., 2012; Tessner et al., 2011).

Such vulnerability to even minor stressors may contribute to the onset and maintenance of psychosis. In a follow-up analysis of their ESM data, Myin-Germeys et al. (2005) reported an association between occurrence of stressors in daily life, and the intensity of psychotic experiences (PEs) in both the clinical group as well as relatives. Similarly, Collip et al. (2013b) used ESM in a general population sample of female twins, and assessed reactivity to daily life stress, subclinical PEs and reactivity to these experiences. Greater affective stress-reactivity and PE reactivity were associated with greater persistence of PEs over a 14-month period. The same group also reported an association of PE persistence with daily stressors in psychosis patients and relatives of psychosis patients (Wigman et al., 2013). Additionally, there is evidence in healthy individuals to suggest that acute psychosocial stress and anxiety-provoking situations increase paranoid ideation (Kesting, Bredenpohl, Klenke, Westermann, and Lincoln, 2013; Lincoln, Lange, Burau, Exner, and Moritz, 2010) and exacerbate monocausal reasoning and jumping-to-conclusions in psychosis patients with delusions (Moritz, Köther, Hartmann, and Lincoln, 2015). Reininghaus et al. (2016) conducted an ESM study in first-episode psychosis patients and at-risk individuals, showing that elevated stress-sensitivity to daily events as well as increased threat anticipation were associated with greater rates of PEs. Docherty et al. (2009) assessed self-reported trait stress-reactivity in psychosis patients and in healthy controls, and followed both groups over a 9-month period. Patients reported greater trait reactivity at baseline, and stressful life events over the follow-up period predicted psychotic symptoms, with an interaction effect between trait reactivity and number of events. There is now a comprehensive literature that strongly suggests increased threat perception as a key factor in psychosis and need for care, with supporting evidence from self-report, experimental, and neuroimaging studies (Reininghaus et al., 2016; Underwood et al., 2016).
It is possible that early life stress may confer psychosis risk through increasing sensitivity and vulnerability to stress later in life. Indeed, an ESM study in 50 psychosis patients showed that history of childhood trauma was associated with greater reactivity to life stress, and that childhood trauma and stress-reactivity interacted to predict intensity of psychotic experiences (Lardinois, Lataster, Mengelers, van Os, and Myin-Germeys, 2011). Interestingly, evidence from a 10-year prospective cohort study showed that early exposure to adversity increased the risk of adversity exposure in adolescence, which in cases of recent severe adversity interacted additively to increase the risk of psychosis (Lataster, Myin-Germeys, Lieb, Wittchen, and van Os, 2012). Thus, it appears that early life adversity exposure may lay the foundation for greater vulnerability to stressful events in later life, potentially both in terms of increased risk of exposure to adverse events in later life as well as greater reactivity to stress in adulthood. In turn, this heightened stress-sensitivity may then further drive the occurrence and intensity of psychotic symptoms, and the appraisal of innocuous situations and stimuli as threatening.

3.2.2 Stress and the Aetiology of AVHs

Whilst a comprehensive discussion of cognitive models of AVHs is beyond the scope of the current thesis, it is nonetheless noteworthy that evidence also suggests a close link between stress and emergence of AVHs from a cognitive perspective. Current evidence on the cognitive aetiology of AVHs posits that they partially arise due to defective monitoring of inner speech, which gives rise to the interpretation of inner speech as an externally originating, and may also represent failure to inhibit traumatic or stressful memories and information (Allen, Aleman, and McGuire, 2007; Jones, 2010). It has further been suggested that such false detections may arise as a by-product of perceptual hypervigilance induced and maintained by stressful life events and emotional distress (Dodgson and Gordon, 2009). This is in line with research suggesting heightened threat perception in psychosis (Reininghaus et al., 2016; Underwood et al., 2016), as well as evidence of trauma exposure in psychosis and its direct link to AVHs (Bentall et al., 2012; Hardy et al., 2016; Shevlin et al., 2007; Varese et al., 2012). Further, experimental evidence
shows that psychological stress increases false auditory perceptions in a signal detection task where participants are asked to detect speech in white noise, particularly in individuals with higher trait anxiety (Hoskin, Hunter, and Woodruff, 2014). Whilst specific subtypes of AVHs may rely on different causal mechanisms (Dodgson and Gordon, 2009; Smailes et al., 2015), early stress exposure may shape an on-going sensory sensitivity biased to quickly identify potential threats, which then, maintained by emotional distress and hypervigilance, leads to the misidentification of internal verbal events as auditory perceptions.

3.2.3 Physiological Stress-Function in Psychosis

3.2.3.1 The Autonomic Nervous System

In line with evidence on stress exposure and stress-reactivity, there is now a considerable evidence-base to suggest altered physiological stress-function in psychosis, indicative of allostatic load. This appears to be the case for both the HPA axis and the ANS, and alterations of the stress system have been found both at rest and under acute stress exposure. However, as noted by Holtzman et al. (2013), the HPA axis has received more attention, primarily due to the relatively less invasive methods available for its measurement. Nonetheless, several alterations of the ANS have also been demonstrated. A recent review of the ANS literature in psychosis noted that activity of the sympathetic branch of the nervous system appears to operate at normal levels in clinical individuals, whereas activity of the parasympathetic branch is dampened, establishing an imbalance in ANS activity (Montaquila et al., 2015). The two primary measures that have been employed to detect such an imbalance are heart rate variability (HRV) and vagal tone (VT). HRV describes slight arrhythmia of cardiac activity, specifically of the R component, i.e., the upward deflection, in the QRS curve that describes the heartbeat. Although it may be commonly assumed that the QRS curve occurs at regular intervals, there is a complex chaotic rhythmicity. Such mathematical patterns are observed in a variety of biological systems, and they are thought to increase adaptability, in the case of HRV conferring cardiac ability. If there is always slight variation in R intervals, the cardiovascular system optimises its ability to
flexibly adapt to sudden change in demands, such as onset of a stressor. HRV further synchronises with respiratory function, a phenomenon called respiratory sinus arrhythmia (RSA), in that exhalation is accompanied in a slowing of heart rate, whereas inhalation sees an increase. RSA and HRV are used as a proxy to measure vagal tone, and thus PNS activity.

So far, more than a dozen studies have demonstrated diminished vagal tone, and thus PNS dysfunction, in schizophrenia (Montaquila et al., 2015). Further, several studies have provided evidence that diminished PNS activity is associated with psychotic symptom severity and illness duration (Bär et al., 2005; Okada, Toichi, and Sakihama, 2003; Toichi et al., 1999). Whilst decreased HRV has been demonstrated in unmedicated psychosis patients (Bär et al., 2012; Mujica-Parodi, Yeragani, and Malaspina, 2005), antipsychotics have been reported to exacerbate ANS imbalance (Birkhofer et al., 2013; Huang et al., 2013), although one study also found normalisation of PNS activity following six weeks of risperidone treatment (Chang et al., 2010). There is further evidence to suggest that in response to stress, increases in SNS activity of psychosis patients do not differ from those of healthy controls, however recovery of vagal tone and ANS balance fail to initiate following cessation of exposure to the stressor (Akar, Kara, Latifoğlu, and Bilgiç, 2014; Castro et al., 2008; Jaüregui, 2011). Accordingly, skin conductance response to stress has been shown to be increased in psychosis (Lincoln, Hartmann, Köther, and Moritz, 2015; Zahn and Pickar, 2005). It has been proposed that this sluggish stress recovery finds its substrate in inadequate PNS activity which leads to SNS dominance in the ANS (Montaquila et al., 2015). Thus, the ANS in psychosis patients may be conceptualised as a state of constant arousal, stemming from the uneven balance of the SNS and PNS. Indeed, there is evidence to suggest that schizophrenia patients also show significantly faster and more shallow respiration compared to controls and healthy relatives (Bär et al., 2012). These respiratory patterns are associated with severity of positive symptoms (Bär et al., 2012). Bär et al. (2012) also carried out a stress-induction in control and healthy relative participants, showing that during acute stress respiratory patterns were comparable to those seen in patients. Additionally, Clamor and colleagues (2014) reported that that ANS alteration in psychosis, including HRV
measures and vagal tone, are not present in first-degree relatives of psychosis patients, or individuals with attenuated positive symptoms. However, there have also been reports of alterations to HRV in healthy relatives of schizophrenia patients (Bär et al., 2012).

Salivary α-amylase is a further biomarker that has been increasingly employed in stress research to measure ANS activity. It is responsive to psychosocial stress paradigms, with its reactivity preceding the slower onset of HPA activity (Nater et al., 2004). Some studies have reported a significant correlation of peripheral noradrenaline and α-amylase in response to stress (Chatterton, Vogelsong, Lu, Ellman, and Hudgens, 1996; Rohleder, Nater, Wolf, Ehlert, and Kirschbaum, 2004), however such findings have not always been replicated (Nater et al., 2006; Wetherell et al., 2006). Indeed, salivary glands are under control of both sympathetic and parasympathetic nerves (Proctor and Carpenter, 2007), and α-amylase may more accurately reflect overall ANS activity. Accordingly, there is some evidence for a negative association of α-amylase and PNS activity, as measured by changes to HRV and vagal tone (Bosch, de Geus, Veerman, Hoogstraten, and Nieuw Amerongen, 2003; Nater et al., 2006). Such evidence is consistent with the two studies that have considered α-amylase as a biomarker in schizophrenia. Inagaki et al. (2010) measured α-amylase and resting heart rate in 54 schizophrenia patients and 55 controls, showing that whilst heart rate did not differ, α-amylase levels were significantly higher in clinical participants. Moreover, α-amylase levels were significantly correlated with symptom severity. Ieda et al. (2014) elaborated on these findings in 25 schizophrenia patients and 25 controls. In addition to α-amylase, the study investigated both low frequencies of heart rate variability and ratio of low frequency to high frequency, reflecting PNS and SNS activity, respectively. Again, patients showed significantly higher levels of α-amylase, which correlated with symptom severity. However, the study also showed lower levels of HRV frequencies related to PNS activity in patients, yet no changes to SNS activity. Thus, α-amylase levels in psychosis patients seem to reflect the imbalance of the sympathetic and parasympathetic branches of the ANS.
Alterations of several HPA axis measures have been found in psychosis, including baseline function, acute stress-reactivity, cortisol awakening response, morning cortisol, and negative feedback function. However, the evidence is often marked by mixed results, associations with clinical presentation remain unclear and psychotropic treatments may confound findings.

There is some evidence for higher baseline HPA activity, as indicated by increased cortisol levels in psychosis patients compared with controls. A systematic review by Bradley and Dinan (2010) reported evidence for increases in basal cortisol levels in schizophrenia patients, most consistently so in first-episode and drug-naive patients. Moreover, a recent study has reported higher hair cortisol levels (an indicator of long-term HPA activity) in drug-naive first episode patients (Andrade et al., 2016). In a study comparing 256 high-risk individuals to 141 healthy controls, Walker et al. (2013) demonstrated greater cortisol levels in the high-risk group, as well as higher cortisol levels in those who transitioned to a psychotic disorder compared with high-risk individuals who did not transition. Thus, baseline HPA activity appears to be augmented in psychosis. However, it remains unclear whether and how increased cortisol release relates to clinical characteristics of symptoms, with generally mixed and inconsistent findings across the literature (Bradley and Dinan, 2010). Bradley and Dinan (2010) also identified five studies that examined CRH levels in the cerebrospinal fluid of patients and controls, as well as another 17 that measured ACTH, showing overall inconclusive evidence. Thus, whilst cortisol release may differ in psychosis, other components of the HPA axis appear unaffected. Moreover, some research has proposed that increased HPA activity of psychosis patients may be reflected in greater size of the pituitary gland, yet a recent meta-analysis of 10 studies including first episode patients, patient with diagnoses of schizophrenia or schizotypal disorders and/or ultra high-risk individuals found inconclusive results compared with healthy controls (Nordholm et al., 2013).

There is some evidence for a blunted cortisol response to acute stress exposure in psychosis, although the literature is small and findings have been equivocal. Ciufolini et al. (2014)
performed a meta-analysis of three studies measuring the HPA response to acute social stress paradigms. Although their findings should be considered cautiously in light of the small number of studies included in the analysis, they found a blunted cortisol response in schizophrenia patients both in anticipation of and exposure to the stressor. In a systematic review of studies measuring subjective, HPA and heart rate responses to psychosocial stress tasks in schizophrenia patients, Lange et al. (2016) concluded that whilst subjective responses did not differ significantly from controls, heart rate increases were significantly greater in patients. Regarding cortisol response, they noted that while some studies showed differences, overall the findings on HPA response were somewhat inconclusive. However, Goldman et al. (2007) reported a blunted cortisol and ACTH response to the cold pressor paradigm, whereby a stress response is triggered through submersion of a limb in ice-cold water, in schizophrenia patients compared to controls. Another recent study utilising the cold pressor paradigm, together with a psychosocial stress element (being observed and filmed during the cold pressor; Socially Evaluative Cold Pressor Test), found a smaller cortisol response in schizophrenia patients compared to controls (Rubio et al., 2015). Similarly, Pruessner et al. (2013) found that individuals at high clinical risk showed an attenuated HPA response when exposed to a social stress paradigm. Interestingly, a recent study by Lincoln and colleagues showed that psychosis patients showed blunted cortisol levels in response to both social and noise stress compared to individuals with attenuated psychotic symptoms, but not healthy controls (Lincoln, Köther, Hartmann, Kempkensteffen, and Moritz, 2015). A further contradictory finding was obtained by Nugent et al. (2015), who introduced the option for participants in their schizophrenia sample to stop the experiment’s stress task, in order to assess distress intolerance. In that study, the cortisol response was augmented in those participants who showed low distress tolerance and prematurely quit the task. There is also some evidence that the attenuated stress response may be partially due to antipsychotic use. Houtepen et al. (2015) measured cortisol and alpha-amylase responses to the TSST in euthymic bipolar disorder patients, unaffected siblings and healthy controls. Patients showed a blunted cortisol stress response, yet an increased response of alpha-amylase.
Separating patients based on antipsychotic use, the study found that the cortisol response only differed from controls in those patients receiving antipsychotic treatment, independent of other clinical characteristics.

A recent meta-analysis further reported on 44 studies comparing morning cortisol levels in psychosis samples to healthy controls, showing significantly increased morning cortisol levels in clinical individuals (Girshkin, Matheson, Shepherd, and Green, 2014). This effect was less pronounced in first-episode samples, yet greater in medication-free and inpatient samples. Notably however, several studies have also provided evidence for a blunted cortisol awakening response in psychosis patients (Braehler et al., 2005; Mondelli et al., 2010; Monteleone et al., 2014). As the cortisol awakening response represents somewhat of a natural stress response to waking up, this evidence broadly mirrors the evidence obtained on general baseline cortisol levels and acute stress-reactivity. That is, the general pattern appears to show a high baseline output, with a blunted response to acute demand. It remains unclear whether this pattern is due to a ceiling effect of HPA secretion capacity or whether it is due to functional alterations (Holtzman et al., 2013).

Bradley and Dinan (2010) also identified 85 studies that carried out the dexamethasone suppression test (DST) in schizophrenia patients. Dexamethasone is not able to pass the blood brain barrier, but exerts its negative feedback by binding to GRs in the anterior pituitary gland which lies outside the CNS, leading to suppression of ACTH and subsequently cortisol release. Thus, the DST allows at least partial assessment of the HPA axis’ negative feedback capacity. In Bradley and Dinan’s (2010) calculation, non-suppression occurred in 26.9% of medicated patients, and 29.4% of non-medicating patients, suggesting impaired GR-function in both medicated and non-medicating patients. An older meta-analysis reported similar findings, with non-suppression in 26.4% of patients and 5.0% of healthy controls (Yeragani, 1990). As with basal cortisol levels, Bradley and Dinan (2010) report that there were no consistent associations with DST results and clinical characteristics or symptoms. However, nine studies cited by Bradley
and Dinan (2010) administered the DST upon admission and after treatment, all reporting high levels of non-suppression at baseline with large reductions in non-suppression following antipsychotic treatment. Thus, GR-function appears impaired in psychosis, which may be driving the increased baseline activity as well as blunted reactivity to acute demands.

However, there is evidence suggesting that alterations of the HPA axis in psychosis do not present uniformly, but rather depend on individual prior stress exposure. Phassouliotis et al. (2013) conducted a low-dose DST (0.25mg) in first episode patients, finding lower basal morning cortisol and hyper-suppression in response to the DST in patients compared with controls. The authors suggest that this may be related to greater levels of childhood trauma found in the patient group, and indeed this pattern is similar to the HPA function reported in post-traumatic stress disorder (Baumeister et al., 2014). Mondelli et al. (2010) found that the number of stressful life events experienced in their first-episode psychosis sample was negatively correlated with basal cortisol levels, whereas healthy controls showed a positive correlation. Similarly, Braehler et al. (2005) reported lower basal cortisol levels in patients with childhood trauma experience compared to patients with no exposure. Thus, idiosyncratic patterns of HPA activity may vary depending on variables associated with prior stress exposure rather than being associated with clinical diagnoses.

Finally, whilst the neural diathesis-stress model of schizophrenia proposes that the HPA axis mediates the relationship between stress and psychotic symptoms (Pruessner, Cullen, Aas, and Walker, 2017; Walker, Mittal, and Tessner, 2008; Walker and Diforio, 1997), little evidence suggests associations of aberrant HPA activity and specific psychotic symptoms or their severity (Pruessner et al., 2017). This may be due to a) a non-specific effect of HPA-axis dysregulation in psychosis, or b) the inability of cross-sectional research designs to find such effects due to confounding effects of medication, diagnostic criteria and limited symptom severity ranges in psychosis research studies (Pruessner et al., 2017). Indeed, despite the recommendation to move away from diagnostic classification systems towards symptom-oriented research (Insel et
al., 2010), the present review failed to identify any studies that selected psychosis samples based on a specific symptom, e.g., AVHs. Given that psychosis is a multifactorial construct, where individual symptom dimensions may be associated with specific neurophysiological substrates (e.g., striatal dopamine dysregulation and delusional ideation; Howes et al., 2013; Howes and Kapur, 2009; Howes et al., 2012), HPA-axis function may be associated with specific symptoms too. In light of the evidence reviewed above, such an association may be particularly likely for the AVH dimension.

3.3 Conclusions and Implications for Voice-Hearer Research

There is considerable evidence to suggest that psychosis is closely linked with altered stress-exposure, -reactivity and -physiology. Childhood trauma elevates psychosis risk and sensitises to stressful events in later life, with greater subjective stress-reactivity in psychosis patients. Moreover, both major branches of the physiological stress system appear altered in psychosis patients, suggesting that subjective changes in stress-function are accompanied by allostatic load. In several but not all studies, such changes were found to be associated with positive symptoms and symptom severity. None of the studies identified here investigated stress-function specific to voice-hearers. However, the strong link between childhood trauma and AVHs, as well as childhood trauma and dysregulated stress-function, suggests that AVHs in psychosis may be associated with alterations of the HPA and ANS systems. Thus, it is warranted to investigate the particular role that subjective and physiological stress-function may play in the impact of voice-hearing.
Chapter 4 – Need for Care, Adversity Exposure and Perceived Stress in Clinical and Healthy Voice-Hearers

This chapter utilised an existing dataset collected as part of a wider study (the UNIQUE study, Peters et al, 2016). The doctoral candidate’s contribution to the present chapter is the conceptualisation of the research question, identification, selection and scoring of relevant variables and participant sub-samples in the dataset, all statistical analyses, and interpretation of findings to address the research question.

4.1 Introduction

As reviewed in Chapter 3, early life adversity, such as childhood, sexual and physical abuse, has been linked to psychosis as a potential risk factor (Read, van Os, Morrison, and Ross, 2005; Varese et al., 2012), with some evidence for a dose-dependent relationship between exposure and psychosis risk (Read et al., 2005; Varese et al., 2012). Diathesis-stress models propose that vulnerability factors, such as genetic predisposition, interact with exposure to stressors in the origin and maintenance of psychotic symptoms and disorders (Nuechterlein and Dawson, 1984; Walker and Diforio, 1997). Systematic reviews have identified several alterations of physiological stress-function in psychosis, including increased autonomous nervous system activity (Montaquila et al., 2015), and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Bradley and Dinan, 2010). Similarly, experience sampling methods have demonstrated that psychosis patients are more likely to appraise daily stressors as more stressful than first-degree relatives and healthy controls (Myin-Germeys et al., 2001), and history of childhood trauma in psychosis is associated with greater reactivity to life stress (Lardinois et al., 2011). Evidence further points to an gene-environment interaction between HPA-related risk alleles and adversity exposure in the emergence of psychosis risk (Collip et al., 2013a; Cristóbal-Narváez et al., 2016).
In recent work on diathesis-stress models, the potential difference between early stressful life events and risk exposure later in life is highlighted, suggesting that the emergence of psychosis depends on the combination of three ‘hits’: genetic vulnerability, adverse childhood experiences and subsequent adolescent/adult experiences (Daskalakis et al., 2013). There is robust evidence for the diathesis-stress conceptualisation in psychosis populations (Collip et al., 2013a; Howes, McCutcheon, Owen, and Murray, 2016; Varese et al., 2012), and increasingly this relationship is being investigated along the psychosis continuum (Chapter 2; Binbay et al., 2012; Peters et al., 2016). As reviewed in Chapter 2 of this thesis, a novel line of research has identified and investigated the phenomenon of psychotic experiences in otherwise healthy populations (Johns et al., 2014; Peters et al., 2016). Auditory verbal hallucinations, once stipulated as a hallmark symptom of psychotic disorders such as schizophrenia (Schneider and Kurt, 1959), have an estimated prevalence of 5-6% in the general population (Linscott and van Os, 2013; McGrath et al., 2015). Approximately 12% of these individuals may hear voices persistently (De Loore et al., 2011; Linscott and van Os, 2013). Although they have a higher risk of developing a psychotic disorder, nevertheless the majority suffer no distress or impairment as a result of their voices (Chapter 2; Johns et al., 2014). Research comparing clinical (CVH) and healthy voices-hearers (HVH) has identified a number of specific similarities and differences (Chapter 2; Johns et al., 2014). The two groups do not differ on several phenomenological characteristics, such as loudness, perceived location or number of voices. However, voice content is more negative in CVHs, frequency is higher, and beliefs about voices are more negative (see Chapter 2). On other parameters, such as functioning or cognitive biases for psychosis, HVHs show some deficits relative to healthy controls without voices (HCs), although these remain subclinical and are significantly lower than CVHs (see Chapter 2). Notably, the dopamine dysregulation seen in psychosis is absent in HVHs, as demonstrated in a positron-emission tomography study investigating dopamine synthesis capacity (Howes et al., 2013).

Early life adversity, particularly sexual abuse, is associated with the emergence of auditory verbal hallucinations (AVHs) in psychosis (Bentall et al., 2012; Hardy et al., 2016; Shevlin et al.,
2007). Given the strong evidence for diathesis-stress models in psychosis and AVHs specifically, several studies have investigated childhood trauma as well as familial risk in HVHs (the first two “hits” of the three hit model). Data from the biggest cross-sectional study of CVHs (n = 100) and HVHs (n = 127) to date suggest that childhood sexual, physical and emotional abuse, and physical and emotional neglect, do not differ in voice-hearing groups, and are consistently more prevalent than in healthy controls (HCs; n = 124) (Daalman et al., 2012b; Sommer et al., 2010a). However, other (albeit smaller) studies have reported slightly higher rates in CVHs than in HVHs, although childhood trauma rates are still considerably higher than in HCs (Honig et al., 1998). One study in particular found no overall differences in trauma exposure, but higher rates of childhood sexual abuse in CVHs (Andrew et al., 2008). The only study considering lifetime exposure (i.e., combined childhood and adulthood) reports higher rates in HVHs than in HCs, but lower rates than in CVHs (Kråkvik et al., 2015). Similarly, rates of psychotic disorders in first- and second-degree relatives do not differ between CVHs and HVHs, but are higher than in HCs (van Lutterveld et al., 2014). HVHs also report significantly higher rates of familial depressive disorders, mania and substance misuse than HCs (Sommer et al., 2010a). Together, these findings suggest that diathesis-stress models are also relevant for the emergence of AVHs across the psychosis continuum, but raise the important question as to why need for clinical care and the impact of voices differ despite seemingly similar risk factor exposure.

One potential explanation is that the time-period for exposure to trauma as a risk factor for psychosis extends beyond childhood trauma. In the three-hit model, the timing of adversity exposure, and, specifically, adversity exposure in adolescence/adulthood (i.e., the third “hit”) is of crucial importance to developmental trajectories (Daskalakis et al., 2013). Furthermore, factors other than exposure to victimisation, such as cannabis and substance abuse, which are strongly implicated in psychosis (Large, Sharma, Compton, Slade, and Nielssen, 2011; Marconi, Di Forti, Lewis, Murray, and Vassos, 2016), adversely impact on stress physiology (Huizink, Ferdinand, Ormel, and Verhulst, 2006), and may also act as adversity exposure in the third “hit” (Daskalakis et al., 2013). Such factors have not been investigated in HVHs. The biological stress
literature further suggests that the conceptualisation of childhood as anything before 18 years of age may conflate distinct periods in stress-function (Casey, 2013; Daskalakis et al., 2013; Stroud et al., 2009), and a more detailed analysis of adversity exposure is needed.

More chronic stressors, such as socioeconomic deprivation or discrimination in childhood and adulthood, have been identified as risk factors in psychosis (Kristensen, Gravseth, and Bjerkedal, 2010; Oh, Cogburn, Anglin, Lukens, and DeVylde, 2016; Saleem et al., 2014; Veling et al., 2007; Werner, Malaspina, and Rabinowitz, 2007), but have also not been investigated in HVHs. Yet the physiological impact of episodic stressors is contingent on the context of chronic stress, with an interaction of episodic and high chronic stress being associated with HPA alterations typical for psychosis (Marin et al., 2007). The psychological literature further suggests that repeated adversity exposure and social defeat (Birchwood, Meaden, Trower, Gilbert, and Plaistow, 2000; Selten, van der Ven, Rutten, and Cantor-Graae, 2013) are crucial in forming cognitive schema of low social-rank, including in relation to voices (Paulik, 2012), and are associated with the development of paranoid ideation (Valmaggia et al., 2015). Given the impact of early adversity exposure on severity of disturbances in psychosis (Read, 1998; Read et al., 2005) and the evidence that adversity exposure contributes to increased stress-reactivity in psychosis (Lardinois et al., 2011), the question is raised as to whether and which adversity exposure predicts need for care and stress-reactivity in voice-hearers. Indeed, it is unclear whether need for care arises through repeated exposure to the same types of adversity, or through exposure to different adversity types at different time points.

The present study set out to investigate whether CVHs and HVHs differ in their exposure to the three ‘hits’. In line with the stress literature, childhood hits were defined as those occurring at or before age 13 and adolescent/adult hits as those occurring from age 13 (Stroud et al., 2009). The hits were defined as:

I. Hit 1: familial risk (comprising family history of psychosis, and family history of mood, anxiety and substance use disorders)
II. Hit 2: childhood adversity exposure (comprising childhood sexual trauma, non-sexual trauma, discrimination and childhood socio-economic status (SES))

III. Hit 3: adolescence and adulthood adversity exposure (comprising adolescent/adult sexual trauma, non-sexual trauma, discrimination, adult SES, and cannabis and other substance abuse)

Based on the available evidence, it was hypothesised that CVHs would not differ from HVHs in their exposure to Hits 1 and 2, but would significantly differ in their exposure to Hit 3, as presented in Figure 4.1.

To investigate whether adversity exposure contributes to stress-reactivity and -sensitivity, the association of adversity exposure with perceived stress within each hit was also investigated. In line with the first hypothesis where Hit 3 differentiates CVHs and HVHs, it was hypothesised that exposure in Hit 3 would be significantly associated with perceived stress.

Figure 4.1 – Proposed risk/adversity-exposure for CVHs and HVHs at each hit
4.2 Methods

4.2.1 Sample

The sample comprised 57 CVHs and 45 HVHs. Sample characteristics are presented in Table 4.1. Both groups were recruited from south London and north Wales, as part of the wider Unusual Experiences Inquiry (UNIQUE) study (Peters et al., 2016), and were selected if they had current AVHs, as indicated by a score of ≥2 on the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984) AVH item. Clinical participants were recruited from inpatient and outpatient services in the same regions of south London and north Wales (the South London and Maudsley NHS Foundation Trust (SLaM) and the Betsi Cadwaladr University Health Board (BCUHB) respectively). Non-clinical participants were recruited through specialist sources, such as spiritual organisations, in the community (described in Peters et al. (2016) in more detail).

For clinical participants to be included, they had to have: a) a diagnosis of a psychosis spectrum disorder (ICD-10 F20-39 diagnoses). For non-clinical participants, they had to present with: a) absence of psychosis diagnosis or treatment; b) presence of psychotic experiences for at least five years (to avoid recruitment of prodromal individuals); c) no voice-related distress, as indicated by a score of <2 (‘unmet need’) on the Camberwell Assessment of Need (Phelan et al., 1995) ‘psychological distress’ item. Both groups had to: a) be above 18 years old; b) have sufficient command of the English language; c) have no history of neurological disease, brain injury or epilepsy, and d) have no primary substance dependence.

4.2.2 Measures

4.2.2.1 Victimisation Experiences Schedule

The Victimisation Experiences Schedule (VES) was developed as part of the UNIQUE study (Peters et al., 2016). The measure was used to assess frequency, duration and subjective impact of 14 victimisation items grouped into three categories (presented in Table 4.1). Sexual victimisation was assessed on three items (e.g., unwanted sexual intercourse), non-sexual
victimisation was recorded on six items (e.g., physical abuse), and discrimination was assessed on five items (e.g., being treated unfairly by the police). For each item, up to three potentially discrete events were recorded. Further information was recorded for each event on: age at exposure; frequency of exposure (scored 0-4; ranging from “Never” to “Very Frequently (weekly +)”; duration of exposure (scored 0-4; ranging from “Never” to “More than one year”); and impact at the time of exposure (phrased as “How much did this event/experience affect you at the time?”, scored 0-4; ranging from “Not at all” to “Totally”). Total possible ranges of scores for each frequency, duration and impact were 0-36 for sexual victimisation, 0-72 for non-sexual victimisation and 0-60 for discrimination. Total overall scores are presented in Table 4.2.

To create an indicator of severity, a composite score for each victimisation category was calculated, adding frequency, duration, and impact scores. Any event occurring age 13 and below represented the first hit (Childhood sexual victimisation; Childhood non-sexual victimisation; Childhood discrimination), and events occurring above age 13 represented the second hit (Adulthood sexual victimisation; Adulthood non-sexual victimisation; Adulthood discrimination).

<table>
<thead>
<tr>
<th>Table 4.1 – VES subscales</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Victimisation Type</strong></td>
</tr>
<tr>
<td>Sexual victimisation</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Non-sexual victimisation</td>
</tr>
<tr>
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<tr>
<td></td>
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<tr>
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<tr>
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<tr>
<td>Discrimination</td>
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</tr>
</tbody>
</table>
A Principal Component Analysis was carried out to determine whether the VES scales based on frequency, duration and impact represented a latent factor indicative of a general severity of victimisation exposure. The Kaiser-Meyer-Olkin measure verified sampling adequacy of all scales and Bartlett’s test of sphericity indicated sufficiently large correlations of all scales (see Table 4.2). All scales had an eigenvalue over the Kaiser’s criterion of 1. Since no item had a coefficient below 0.5, all items were included, with the lowest factor loading being 0.92. Cronbach’s α indicated good or excellent reliability for all items (lowest was 0.87).
Table 4.2 – Validity and reliability analyses for VES scales (frequency + duration + impact scores)

<table>
<thead>
<tr>
<th>Scale</th>
<th>KMO</th>
<th>Bartlett’s test</th>
<th>Eigenvalue</th>
<th>Explained Variance</th>
<th>Lowest Factor Loading</th>
<th>Cronbach’s α</th>
<th>Score Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood sexual victimisation</td>
<td>.77</td>
<td>$\chi^2 (3) = 411.1, p &lt; 0.001$</td>
<td>2.84</td>
<td>94.6%</td>
<td>.96</td>
<td>.96</td>
<td>0-108</td>
</tr>
<tr>
<td>Childhood non-sexual victimisation</td>
<td>.74</td>
<td>$\chi^2 (3) = 519.3, p &lt; 0.001$</td>
<td>2.88</td>
<td>96.0%</td>
<td>.97</td>
<td>.98</td>
<td>0-216</td>
</tr>
<tr>
<td>Childhood discrimination</td>
<td>.74</td>
<td>$\chi^2 (3) = 498.2, p &lt; 0.001$</td>
<td>2.86</td>
<td>95.2%</td>
<td>.96</td>
<td>.97</td>
<td>0-180</td>
</tr>
<tr>
<td>Adulthood sexual victimisation</td>
<td>.72</td>
<td>$\chi^2 (3) = 399.7, p &lt; 0.001$</td>
<td>2.75</td>
<td>91.5%</td>
<td>.92</td>
<td>.96</td>
<td>0-216</td>
</tr>
<tr>
<td>Adulthood non-sexual victimisation</td>
<td>.74</td>
<td>$\chi^2 (3) = 410.4, p &lt; 0.001$</td>
<td>2.80</td>
<td>93.2%</td>
<td>.94</td>
<td>.87</td>
<td>0-432</td>
</tr>
<tr>
<td>Adulthood discrimination</td>
<td>.77</td>
<td>$\chi^2 (3) = 393.4, p &lt; 0.001$</td>
<td>2.83</td>
<td>94.2%</td>
<td>.96</td>
<td>.96</td>
<td>0-360</td>
</tr>
</tbody>
</table>
4.2.2.2 Scale for the Assessment of Positive Symptoms

The SAPS (Andreasen, 1984) is a 35 item scale, comprising four subscales: hallucinations, delusions, bizarre behaviour and thought disorder. Each item is scored from 0-5 for severity and frequency (“none” to “severe”), leading to a total range of scores from 0-175. Cronbach’s $\alpha$ in the present study indicated good reliability (0.84).

4.2.2.3 Appraisal of Anomalous Experiences Interview

The Appraisal of Anomalous Experiences Interview (AANEX; Brett et al., 2007)) is a semi-structured interview used to measure psychotic experiences in clinical and non-clinical samples. Seventeen anomalous experiences, including AVHs, are rated for lifetime and current (last month) presence on a 3-point scale (1=not present; 2=unclear; 3=present). Whilst the measure also assesses context, appraisal and cognitive responses associated with anomalous experiences (AANEX-CAR), only items assessing presence of experiences (AANEX-Inventory) were utilised in the present study.

4.2.2.4 Demographic Assessment

A demographic assessment was carried out to obtain information on: age, gender, ethnicity, years in education, occupation of head of house in childhood, past drug use, current medications, family history of psychosis, family history of other mental health diagnoses (including depression, anxiety, obsessive-compulsive disorder, bipolar disorder and substance use disorders), diagnosis, number of admissions and inpatient status. Years in education were used as a proxy for adulthood SES, as these are not confounded by disorder-related disability and unemployment (Kristensen et al., 2010). Occupation of head of house in childhood was used as a proxy for childhood SES (as in Peters et al. (2016)). Past drug use was recorded separately for cannabis use and use of other substance (excluding alcohol and tobacco), using frequency on a range from 0-5 (“never” to “daily”).
4.2.2.5 Perceived Stress Scale

The Perceived Stress Scale (PSS) 10-item version (Cohen and Williamson, 1988; Roberti, Harrington, and Storch, 2006) was used to measure levels of perceived stress in the last month. Each item (e.g., “How often have you felt nervous or stressed?”) was scored on a 5-point Likert scale ranging from “never” to “very often”), with a potential score range of 0-40 and higher scores representing higher levels of perceived stress. Cronbach’s α in the present study indicated excellent reliability (0.91).

4.2.3 Procedure

Ethical approval was granted by the NRES Committee London Westminster (reference 12/LO/0766) and the SLaM/Institute of Psychiatry (reference R&D2012/047) and CBUHB (reference Jackson/LO/0766) R&D Offices.

Following screening by research workers (either via phone or face to face), participants signed the informed consent form and were assessed on all questionnaire measures, in addition to other experimental procedures not reported here (see Peters et al. (2016) for more detail). Participants were debriefed and compensated for their time, and were offered a follow-up phone call to ensure they suffered no distress due to participation.

4.2.4 Statistical Analysis

Frequentist statistical analyses were carried out using SPSS for Windows (IBM Corp., 2015), and JASP (JASP Team, 2016) was used for Bayesian analysis to express likelihood of data supporting the hypotheses. Bayesian statistics, a statistical method based on estimation of probabilities, were carried out to provide an additional metric to evaluate findings with greater confidence. For the first hypothesis, separate analyses were carried out for each adversity variable (dependent variables); group (i.e., CVH vs HVH) was the independent variable. Chi-square analyses were carried out for binary dependent variables, non-parametric Mann-Whitney U for
non-normally distributed continuous variables, and independent t-tests for normally distributed variables. False Discovery Rate correction for multiple testing was applied to analyses within each hit, and FDR-adjusted p-values are reported throughout (Benjamini and Hochberg, 1995). For the second hypothesis, the association of adversity variables with PSS scores was assessed using three multiple regression models, separating adversity variables by hit, entering group in the first step to control for clinical status, and using bootstrapping (n = 1000) for more conservative and accurate estimation (Tabachnik and Fidell, 1989). P-values below the 0.05 threshold were accepted as statistically significant. Bayes factors of 3 and above were interpreted as sufficient evidence for the alternative hypothesis over the null hypothesis, and Bayes factors of 1/3 and below as sufficient evidence for the null hypothesis (Kass and Raftery, 1995). Calculated effect sizes were converted to Cohen’s d to allow for comparison across effects. Effect size conversions were carried out using formulas commonly used in meta-analyses and research synthesis (Borenstein, Hedges, Higgins, and Rothstein, 2009; Cooper, Hedges, and Valentine, 2009; Fritz, Morris, and Richler, 2012; Lipsey, Wilson, and Lipsey, 2001; Morris and DeShon, 2002).

4.3 Results

4.3.1 Sample Characteristics

Results from analyses of sample characteristics are presented in Table 4.3. CVHs and HVHs did not differ on age, but there were significant differences in gender, ethnicity, and employment. CVHs were more likely to be male and unemployed, and less likely to be of white ethnicity. The two groups also differed in SAPS total score, SAPS AVHs (single item), and perceived stress, with CVHs showing higher scores across all measures. However, groups showed no differences on AANEX total scores for current and lifetime experiences.
Table 4.3 – Sample characteristics (Mean ± SD unless specified otherwise)

<table>
<thead>
<tr>
<th></th>
<th>Clinical Voice-Hearers (n = 57)</th>
<th>Healthy Voice-Hearers (n = 45)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41.7 ± 12.5</td>
<td>45.4 ± 12.5</td>
<td>t (100) = 1.5, p = 0.76, d = 0.30, BF&lt;sub&gt;10&lt;/sub&gt; = 0.5</td>
</tr>
<tr>
<td>Gender (% Female)</td>
<td>38.6%</td>
<td>73.3%</td>
<td>χ&lt;sup&gt;2&lt;/sup&gt; = 12.2, p &lt; 0.001*, d = 0.7, BF&lt;sub&gt;10&lt;/sub&gt; = 70.2</td>
</tr>
<tr>
<td>Ethnicity (% White)</td>
<td>66.7%</td>
<td>91.1%</td>
<td>χ&lt;sup&gt;2&lt;/sup&gt; = 8.6, p = 0.003*, d = 0.6, BF&lt;sub&gt;10&lt;/sub&gt; = 7.5</td>
</tr>
<tr>
<td>Employment (% Unemployed)</td>
<td>82.5%</td>
<td>37.8%</td>
<td>χ&lt;sup&gt;2&lt;/sup&gt; = 21.5, p &lt; 0.001*, d = 1.0, BF&lt;sub&gt;10&lt;/sub&gt; = 11,535.6</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizoaffective Disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis NOS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Affective Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotic Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital Admissions</td>
<td>4.13 ± 3.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Care Status (% Inpatient)</td>
<td>32.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS Total Score</td>
<td>31.8 ± 15.3</td>
<td>15.6 ± 7.4</td>
<td>U = 404.0, Z = -5.8, p &lt; .001*, d = 1.45, BF&lt;sub&gt;10&lt;/sub&gt; = 2.3 x 10&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>SAPS AVH Score</td>
<td>4.2 ± 1.1</td>
<td>2.7 ± 0.9</td>
<td>U = 447.0, Z = -5.9, p &lt; .001*, d = 1.34, BF&lt;sub&gt;10&lt;/sub&gt; = 9.4 x 10&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>AANEX Total Lifetime</td>
<td>36.5 ± 5.1</td>
<td>35.4 ± 5.2</td>
<td>t (99) = 1.0, p = 0.3, d = 0.20, BF&lt;sub&gt;10&lt;/sub&gt; = 0.3</td>
</tr>
<tr>
<td>AANEX Total Current</td>
<td>31.1 ± 6.1</td>
<td>30.4 ± 5.1</td>
<td>t (98) = 0.7, p = 0.5, d = 0.14, BF&lt;sub&gt;10&lt;/sub&gt; = 0.3</td>
</tr>
<tr>
<td>Perceived Stress Score</td>
<td>21.7 ± 7.4</td>
<td>13.4 ± 8.0</td>
<td>t (93) = 5.2, p &lt; 0.001*, d = 1.04, BF&lt;sub&gt;10&lt;/sub&gt; = 12,248.2</td>
</tr>
</tbody>
</table>

Note: * = significant p-value; NOS = Not Otherwise Specified; BF<sub>10</sub> = Bayes Factor (strength of evidence in favour of the tested model over the null hypothesis)
4.3.2 Main Effects of Hit Exposure

Results are presented in Table 4.4. For Hit 1, chi-square showed that a significantly greater percentage of CVHs than HVHs reported a family history of psychosis, but no difference was found for family history of other disorders.

For Hit 2, all variables were non-normally distributed. Mann-Whitney U showed no significant differences on severity scores for childhood sexual victimisation, childhood non-sexual victimisation, and childhood discrimination. The chi-square test showed there was no significant difference in childhood socio-economic status.

For Hit 3, all variables were non-normally distributed. Mann-Whitney U tests showed significant differences for years in education, with CVHs reporting fewer years than HVHs, and for cannabis and other substance use, with a greater percentage of CVHs than HVHs reporting exposure to both variables. No significant differences were found for severity scores on sexual victimisation, non-sexual victimisation, and discrimination. However, HVHs showed trends to greater exposure to sexual (p=0.07) and non-sexual victimisation (p=0.07) in adolescence and adulthood, although this was not corroborated by Bayesian analyses.

Of note, the percentage of individuals reporting victimisation in both childhood and adolescence/adulthood was high in both groups (range 15.8% to 37.8% for sexual, and 66.7% to 82.2% for non-sexual, victimisation), with slightly higher percentages in the non-clinical group for all categories.

Sensitivity analyses using G*Power for Windows (Faul, Erdfelder, Lang, and Buchner, 2007) indicated that the present analyses were powered to detect group difference effect sizes of Cohen’s $d = 0.58$, at $\beta = 0.8$. 


<table>
<thead>
<tr>
<th>Hit Variables</th>
<th>Clinical Voice-Hearers</th>
<th>Healthy Voice-Hearers</th>
<th>Statistical Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hit 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family History Psychosis (%)</td>
<td>25.5%</td>
<td>2.3%</td>
<td>$\chi^2 = 9.5, p = 0.004^*, d = 0.64, BF_{10} = 18$</td>
</tr>
<tr>
<td>Family History Others (%)</td>
<td>15.8%</td>
<td>20.0%</td>
<td>$\chi^2 = 0.3, p = 0.61, d = 0.11, BF_{10} = 0.2$</td>
</tr>
<tr>
<td><strong>Hit 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual Victimisation</td>
<td>15.8%, 12.1 ± 7.1</td>
<td>24.4%, 12.9 ± 8.3</td>
<td>$U = 974, Z = -1.1, p = 0.54, d = 0.42, BF_{10} = 0.3$</td>
</tr>
<tr>
<td>Non-Sexual Victimisation</td>
<td>68.4%, 23.4 ± 17.1</td>
<td>82.2%, 28.0 ± 17.0</td>
<td>$U = 1169.0, Z = -2.1, p = 0.16, d = 0.15, BF_{10} = 1.1$</td>
</tr>
<tr>
<td>Discrimination</td>
<td>8.8%, 14.4 ± 10.5</td>
<td>6.7%, 6.7 ± 1.9</td>
<td>$U = 1249.5, Z = -0.5, p = 0.63, d = 0.05, BF_{10} = 0.3$</td>
</tr>
<tr>
<td>Socio-Economic Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salariat</td>
<td>24.1%</td>
<td>28.6%</td>
<td>$\chi^2 = 5.1, p = 0.61, d = 0.46, BF_{10} = 0.1$</td>
</tr>
<tr>
<td>Intermediate</td>
<td>22.2%</td>
<td>38.1%</td>
<td></td>
</tr>
<tr>
<td>Working class</td>
<td>44.4%</td>
<td>23.8%</td>
<td></td>
</tr>
<tr>
<td>Never worked/long term unemployed</td>
<td>7.4%</td>
<td>7.1%</td>
<td></td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>1.9%</td>
<td>2.4%</td>
<td></td>
</tr>
<tr>
<td><strong>Hit 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual Victimisation</td>
<td>21.0%, 7.7 ± 3.4</td>
<td>37.8%, 10.7 ± 8.5</td>
<td>$U = 1060.0, Z = -1.9, p = 0.07, d = 0.30, BF_{10} = 1.8$</td>
</tr>
<tr>
<td>Non-Sexual Victimisation</td>
<td>66.7%, 16.4 ± 12.1</td>
<td>82.2%, 19.5 ± 14.5</td>
<td>$U = 988.5, Z = -2.0, p = 0.07, d = 0.40, BF_{10} = 1.0$</td>
</tr>
<tr>
<td>Discrimination</td>
<td>63.2%, 18.8 ± 10.9</td>
<td>60%, 19.6 ± 12.9</td>
<td>$U = 1235.0, Z = -0.3, p = 0.74, d = 0.06, BF_{10} = 0.2$</td>
</tr>
<tr>
<td>Years in Education (M±SD)</td>
<td>14.5 ± 4.8</td>
<td>17.3 ± 4.4</td>
<td>$U = 753.0, Z = -3.6, p = .003^*, d = 0.76, BF_{10} = 9.7$</td>
</tr>
<tr>
<td>Cannabis Use</td>
<td>50.9%, 3.1 ± 1.2</td>
<td>26.7%, 2.5 ± 1.4</td>
<td>$U = 930.5, Z = -2.7, p = 0.01^*, d = 0.48, BF_{10} = 7.0$</td>
</tr>
<tr>
<td>Other Substance Use</td>
<td>36.8%, 2.2 ± 1.3</td>
<td>8.9%, 1.5 ± 1.0</td>
<td>$U = 910.5, Z = -3.3, p = 0.003^*, d = 0.51, BF_{10} = 21.9$</td>
</tr>
</tbody>
</table>

Note: * = significant p-value (FDR-adjusted); BF_{10} > 3 supports alternative hypothesis; BF_{10} < 1/3 supports null hypothesis
4.3.3 Relationship between Adversity and Stress

Multiple regression results are presented in Table 4.5. Group was significantly associated with perceived stress in the first step of the multiple regression models. Multiple linear regressions showed that the two variables in the first hit were associated with perceived stress, explaining 6.8% of the variance after controlling for group. Family history of psychosis, but not family history of other disorders, was related to perceived stress, with individuals with a psychosis family history reporting higher stress. Bayesian analysis confirmed this model as the winning model (marked BF\textsubscript{M} in Table 4.5).

For the second hit, multiple linear regressions also showed that adversity was significantly associated with perceived stress, explaining 6.5% of the variance after controlling for group. However, none of the adversity variables (sexual victimisation, non-sexual victimisation, discrimination and SES) was individually related to perceived stress. However, Bayesian analysis selected a model based only on Group + Sexual Victimisation as the winning model.

For the third hit, multiple linear regression again showed that adversity was significantly associated with perceived stress, explaining 6.5% of the variance after controlling for group. Fewer years in education and greater other substance use, but not cannabis use, sexual victimisation, non-sexual victimisation or discrimination, were individually related to higher perceived stress. However, Bayesian analysis selected a model based only on Group as the winning model. Sensitivity analyses using G*Power for Windows (Faul et al., 2007) indicated that the present regression analyses were powered to associations at effect sizes of \( f^2 = 0.10 \) to \( f^2 = 0.14 \) (depending on the number of predictors used in each model), at \( \beta = 0.8 \).
Table 4.5 – Multiple regression models predicting perceived stress by adversity exposure, separated by each hit

<table>
<thead>
<tr>
<th>Models</th>
<th>Predictors</th>
<th>B</th>
<th>SE B</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hit 1</td>
<td><strong>Step 1</strong> Constant</td>
<td>4.62</td>
<td>2.49</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group</td>
<td>8.52</td>
<td>1.50</td>
<td>0.53*</td>
</tr>
<tr>
<td></td>
<td>( F(1,81) = 32.1 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adj. ( R^2 ) = 0.28</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>( p &lt; 0.001 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Step 2</strong> Constant</td>
<td>4.93</td>
<td>2.47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group</td>
<td>7.51</td>
<td>1.49</td>
<td>0.47**</td>
</tr>
<tr>
<td></td>
<td>( F_C = 4.2 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>( R^2_C = 0.35 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Family History Psychosis</td>
<td>7.01</td>
<td>2.43</td>
<td>0.27**</td>
</tr>
<tr>
<td></td>
<td>( p &lt; 0.001 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Family History Other</td>
<td>1.58</td>
<td>1.95</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>( BF_M = 11.5 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hit 2</td>
<td><strong>Step 1</strong> Constant</td>
<td>4.36</td>
<td>2.47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group</td>
<td>8.42</td>
<td>1.47</td>
<td>0.52*</td>
</tr>
<tr>
<td></td>
<td>( F(1,89) = 32.7 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adj. ( R^2 ) = 0.26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>( p &lt; 0.001 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Step 2</strong> Constant</td>
<td>4.61</td>
<td>3.10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group</td>
<td>8.87</td>
<td>1.48</td>
<td>0.55**</td>
</tr>
<tr>
<td></td>
<td>( F_C = 2.1 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>( R^2_C = 0.07 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sexual Victimisation</td>
<td>0.30</td>
<td>0.15</td>
<td>0.18*</td>
</tr>
<tr>
<td></td>
<td>( p &lt; 0.001 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-Sexual Victimisation</td>
<td>0.04</td>
<td>0.05</td>
<td>0.08*</td>
</tr>
<tr>
<td></td>
<td>( BF_M = 7.0 )</td>
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<tr>
<td></td>
<td>Discrimination</td>
<td>0.40</td>
<td>0.36</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>Socio-Economic Status</td>
<td>-1.12</td>
<td>0.77</td>
<td>-0.13</td>
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<tr>
<td>Hit 3</td>
<td><strong>Step 1</strong> Constant</td>
<td>4.37</td>
<td>2.39</td>
<td></td>
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<tr>
<td></td>
<td>Group</td>
<td>8.53</td>
<td>1.43</td>
<td>0.53*</td>
</tr>
<tr>
<td></td>
<td>( F(1,93) = 35.7 )</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Adj. ( R^2 ) = 0.27</td>
<td></td>
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<tr>
<td></td>
<td>( p &lt; 0.001 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Step 2</strong> Constant</td>
<td>10.46</td>
<td>4.44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group</td>
<td>7.12</td>
<td>1.62</td>
<td>0.44**</td>
</tr>
<tr>
<td></td>
<td>( F_C = 1.5 )</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>( R^2_C = 0.07 )</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sexual Victimisation</td>
<td>0.06</td>
<td>0.15</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>( p &lt; 0.001 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-Sexual Victimisation</td>
<td>-0.01</td>
<td>0.06</td>
<td>-0.01</td>
</tr>
<tr>
<td></td>
<td>( BF_M = 18.3 )</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Discrimination</td>
<td>0.09</td>
<td>0.06</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>Years in Education</td>
<td>-0.31</td>
<td>0.18</td>
<td>0.24*</td>
</tr>
<tr>
<td></td>
<td>Cannabis Use</td>
<td>-0.97</td>
<td>0.56</td>
<td>-0.18</td>
</tr>
<tr>
<td></td>
<td>Other Substance Use</td>
<td>1.92</td>
<td>0.84</td>
<td>0.24*</td>
</tr>
</tbody>
</table>

Note: * = significant p-value (\( \alpha = 0.016 \)), * = best predictor model by \( BF_M \), \( F_C \) = F change, \( R^2_C \) = \( R^2 \) change
4.4 Discussion

4.4.1 Findings

The present study is, to our knowledge, the first comparison of healthy and clinical voice-hearers on a range of different adversity factors over both childhood and adolescence/adulthood. We hypothesised that CVHs and HVHs would differ on their exposure to Hit 3 (adolescence/adulthood), but not Hit 1 (familial risk) and Hit 2 (childhood). The findings provide evidence for differential adversity exposure in CVHs and HVHs in adolescence and adulthood (Hit 3), and suggest that exposure to different types of adversity predicts perceived stress, our proxy measure for stress-sensitivity, in these populations. Specifically, in Hit 3 we found that CVHs had fewer years in education, indicative of a lower SES, and higher levels of cannabis and other substance use. Surprisingly, victimisation and discrimination experiences in Hit 3 did not differ between CVH and HVHs, suggesting that developmental timing and repeated victimisation exposure are less important in need for care than exposure to different types of adversity. Indeed, HVHs reported slightly higher exposure to sexual and non-sexual victimisation in adulthood, albeit at non-significant trend-level. As predicted, there was no difference between the groups in adversity exposure in childhood victimisation. Unlike previous reports (van Lutterveld et al., 2014), CVHs were more likely to have family members with a history of psychosis, although history of other disorders did not differ between CVHs and HVHs.

These findings suggest that the emergence of need for care in voice-hearers may ultimately be due to exposure to different types of stressors, and potentially their interaction, rather than continued exposure to victimisation. Putatively, victimisation and discrimination in childhood and adulthood may not only increase the risk for AVH emergence, but create a vulnerability to the adverse impact of recreational substances. Neurochemically, dopamine dysregulation due to substance misuse may increase the likelihood of maladaptive appraisals of their voices, aberrant salience and delusional ideation (Howes and Kapur, 2009; Howes et al., 2012), which
would concur with previous findings that HVHs do not present with the upregulated dopamine synthesis capacity seen in psychosis (Howes et al., 2013). Alternatively, CVHs may suffer more long-term consequences of victimisation and turn to substance misuse as a coping strategy, which then becomes maladaptive. Victimisation is frequently associated with substance misuse as a coping strategy (Filipas, 2006; Harrison, Fulkerson, and Beebe, 1997), and men are more likely to turn to substance misuse after victimisation experiences (Saladin et al., 2003) yet less likely to disclose their experiences to others (Ullman and Filipas, 2005). Thus, the gender difference in the present sample, which is congruent with the wider HVH literature (see Chapter 2), may partially relate to maladaptive coping strategies that exacerbate need for care.

The finding that CVHs were more likely to have a family history of psychosis contradicts our hypothesis, and further suggests that a specific genetic vulnerability may be a risk factor for need for care in voice-hearers. Nonetheless, it is possible that family history of psychosis may be skewed by intrafamilial culture – in some families, where psychotic diagnoses have been established amongst family members, psychotic experiences may be interpreted as an indicator of mental ill health, and help-seeking is established. In families where they are explained in the context of e.g., spiritual experiences, no contact with mental health services may ever be established, and in fact social support structures such as membership of spiritual groups may emerge.

The multiple regression models showed that family history of psychosis, fewer years in education, and non-cannabis substance use predicted perceived stress after controlling for group. However, Bayesian analysis selected slightly different winning models for Hit 2 (Group + Sexual Victimisation) and Hit 3 (only Group). It has been proposed that stress exposure exacerbates dopaminergic dysregulation, leading to delusional ideation and aberrant salience, and increased distress and need for care (Howes et al., 2016). The present results at least partially suggest that several of the specific types of adversity that CVHs are more exposed to
are also those driving perceived stress and stress-sensitivity, and may explain the differential need for care in voice-hearers both via dopaminergic dysregulation and exacerbated stress-reactivity.

4.4.2 Strengths and Limitations

Strengths included that the assessment of trauma in the present study was highly detailed, considering several types of adversity exposure as well as objective (duration; frequency) and subjective (impact) indicators of severity. Factor analyses further confirmed validity of the employed measure, including the stratification into distinct subscales as well as the severity-based computation of scores. As demonstrated by Varese et al. (2012), the similar rates of reported childhood trauma between prospective and retrospective studies in psychosis suggest that recall is accurate, adding confidence in the reliability of our adversity exposure measure. Further, the assessment of adversity exposure over lifetime allowed for detailed investigation of different developmental periods.

There were several study limitations. The first was that the study design did not permit a direct test of the three-hit model described by Dalskalakis and colleagues (2013); rather, it presents findings related to hypotheses and analyses informed by this framework. Larger scale, epidemiological studies would be needed to test the model directly and investigate cumulative and interaction effects of exposure. A further limitation relates to the validity of several exposure variables. Years in education may be cut short by emerging negative symptoms that prevent continuing education, and may also reflect lower IQ in clinical participants. Although not as heavily biased as adulthood employment as an indicator of SES, this bias may nonetheless confound cause and consequence. Second, the cut-off used for puberty onset is based on population means, yet puberty may occur significantly earlier or later in individuals, and also presents with gender dimorphism (Blakemore, Burnett, and Dahl, 2010). Third, the present study did not record onset of cannabis and substance misuse, and timing and frequency of use
at different ages may alter the impact of substance use. Fourth, as non-clinical participants were selected based on an absence of or low voice-distress, it was not possible to investigate the impact of adversity exposure on voice-distress. Fifth, family history of psychosis may be a suboptimal measure for genetic risk due to shared environments within families. Finally, frequentist and Bayesian analyses were not congruent in the multiple regression models, suggesting that these data have to be considered with caution.

### 4.4.3 Implications and Future Directions

Future research should employ more valid measures of genetic risk, such as heritability or genome-wide association studies, or assessment of identified risk genes that may also interact with stress-function, such as genes coding for the glucocorticoid receptor or the chaperone protein FKBP5 (Collip et al., 2013a). Further, the stratification of clinical and non-clinical voice-hearers undertaken here may exclude individuals who do suffer subclinical distress or who are transitioning from psychosis to recovery. Larger, epidemiological population studies are needed to explore the role of adversity exposure in more diverse voice-hearing samples, and potential additive or interaction effects of adversity types. Whilst the use of a cut-off in adolescence may add validity with regards to development of stress physiology, longitudinal research should be undertaken to more accurately investigate the role of adversity, including cannabis and substance misuse, at different ages.

Given the substantial gender difference in the present sample, as well as the wider literature demonstrating increased psychosis risk associated with male gender (Aleman, Kahn, and Selten, 2003), future research should investigate whether female gender is protective in the interaction with adversity exposure in voice-hearers. It has been hypothesised that the gender imbalance in psychosis is due to protective effects of estrogen and its modulation of dopamine (Gogos et al., 2015) and HPA signalling (Pruessner et al., 2015). The gender difference may also relate to differential use of coping strategies subsequent to adversity exposure, i.e., men may be more
likely to use substances (Saladin et al., 2003), whereas women may be more likely to seek social support (Hunter, Boyle, and Warden, 2004; Ullman and Filipas, 2005). However, male psychosis patients also exhibit more negative symptoms and functional impairments (Chang et al., 2011; Morgan, Castle, and Jablensky, 2008; Scott, 2011), and the differential need for care may therefore relate to greater comorbid symptom severity. Indeed, evidence from a large cohort study suggests that social rank and loneliness mediate the association of social adversity and negative symptoms, but not positive symptoms (Jaya, Ascone, and Lincoln, 2016).

Finally, the present study highlights the importance of adversity types that should be malleable to social interventions, including substance misuse and continuing education, a finding that should explored further in prodromal psychosis intervention research.

### 4.4.4 Conclusions

The present study provides evidence that clinical and non-clinical voice-hearers differ in some types of adversity-, or hit-, exposure in adolescence and adulthood, as well as their family history of psychosis. Exposure to trauma and victimisation across both childhood and adulthood was equally high in both groups, suggesting that repeated exposure may be related to the presence of voices rather than need for care. Instead, the findings suggest that need for care in voice-hearers is associated with cannabis and substance misuse in adolescence and adulthood as well as lower socio-economic status, in the context of potential greater genetic vulnerability. These factors further appear to contribute to perceived stress, and should become targets of future research.
Chapter 5 – The Effects of Voice Content and Mindfulness on Stress Reactivity

5.1 Introduction

Auditory verbal hallucinations (AVHs) are typically distressing for clinical voice-hearers and are associated with poor outcomes (Upthegrove et al., 2016). However, nascent research, reviewed in Chapter 2, has demonstrated that AVHs occur in healthy members of the general public and do not necessarily cause distress or imply need for care (Baumeister et al., 2017; Johns et al., 2014), raising the question as to why distress varies between clinical and non-clinical voice-hearers. As reviewed in Chapter 3, psychosis is linked to increased subjective reactivity to stress (Myin-Germeys and van Os, 2007), altered function of both the hypothalamic-pituitary-adrenal axis (Bradley and Dinan, 2010; Pruessner et al., 2017) as well as the autonomous nervous system (Montaquila et al., 2015), and it has been argued that early life stress, in particular, contributes to the aetiology of psychosis and AVHs (Bentall et al., 2012; Varese et al., 2012). Moreover, stress exposure and heightened stress-reactivity in psychosis patients can exacerbate the intensity of psychotic experiences (Myin-Germeys and van Os, 2007; Reininghaus et al., 2016), and differential distress of voice-hearers may therefore be partially related to stress-reactivity and function.

As reviewed in Chapter 2, a consistent finding in the literature is that clinical voice-hearers (CVHs) experience predominantly negative voice content, whereas healthy voice-hearers (HVHs) typically report neutral or positive voice content (Baumeister et al., 2017; Johns et al., 2014). Several studies have further reported that voice content is associated with negative appraisals and mood states, as well as service use and need for care (Beavan and Read, 2010; Daalman et al., 2011a; Johns et al., 2014). Within clinical populations, greater negative voice content is associated with more voice-distress, depression, and low self-esteem (Smith et al., 2006). It has been argued that negative voice content may be crucial in driving the pathological impact of
voice-hearing in CVHs relative to HVHs (de Leede-Smith and Barkus, 2013). Thus, negative voice content may contribute to the distress experienced by CVHs, and exacerbate the impact of stressful situations.

Cognitive models of psychosis have also highlighted the importance of the appraisal of anomalous experiences in determining their impact (Chadwick and Birchwood, 1994; Garety, Kuipers, Fowler, Freeman, and Bebbington, 2001). Several studies have provided evidence that mindful appraisals of voices, that is, experiencing them with present-moment awareness, a non-judgmental attitude and ultimately acceptance, is negatively associated with voice-distress and mood problems, and positively associated with quality of life (Chadwick et al., 2016; Chadwick, Hughes, Russell, Russell, and Dagnan, 2009; López-Navarro et al., 2015; Morris, Garety, and Peters, 2014; Shawyer et al., 2007). Reductions in voice-distress and improvements in mood have been reported as a result of mindfulness-based intervention studies (Chadwick et al., 2009; López-Navarro et al., 2015), and trait mindfulness is higher in non-clinical individuals who report psychotic experiences (Peters et al., 2016). Furthermore, mindfulness is associated with lower subjective and physiological stress-reactivity (Brown, Weinstein, and Creswell, 2012; Bullis, Øe, Asnaani, and Hofmann, 2014; Daubenmier, Hayden, Chang, and Epel, 2014). Thus, whilst it is likely that there is a direct impact of voice content on distress and stress-reactivity, these responses may be moderated by ‘mindful’ voice-appraisals.

In view of this evidence we aimed to test the effect of simulated voices and their content on stress-reactivity. We hypothesised that simulated AVHs with negative voice content would increase the subjective, cortisol and α-amylase reaction to a psychosocial stress paradigm over and above the levels produced by neutral voices or a non-voice ambient control. The latter two were hypothesised not to differ. It was further hypothesised that mindful appraisals of voices during the paradigm (assessed post-hoc) would be associated with attenuated subjective, cortisol and α-amylase stress response.
5.2 Methods

5.2.1 Sample

The sample consisted of 84 healthy participants, with a mean age of 26.1 (SD = 7.2) and predominantly female individuals (n = 62, 73.8%). Participants were primarily recruited through opportunity sampling via online adverts and the King’s College London research recruitment system. Participants were excluded if they: were under the age of 18, were not fluent English speakers, had hearing impairments, had previously experienced auditory hallucinations, had received secondary care for any mental health issue, or scored 10 or above on the depression subscale of the Hospital Anxiety and Depression Scale (HADS). The latter two eligibility criteria were decided upon to exclude vulnerable individuals. Ethical approval for the research study was granted by the King’s College London Psychiatry, Nursing & Midwifery Research Ethics Sub-Committee (ref. PNM/14/15-111; Appendix I).

5.2.2 Measures

5.2.2.1 Montreal Imaging Stress Task

The Montreal Imaging Stress Task (MIST; Dedovic et al., 2005) is a well-established paradigm designed for computerised psychosocial stress induction. In the current study, participants were presented with arithmetic exercises on a laptop for a total of 10 minutes. The computer algorithm adapts to the individual’s ability to perform maths by making the task always a bit harder (both in task difficulty and allotted time) than what the participant is capable of solving so that the individual performs poorly, but not so poorly that it becomes obvious that the task is impossible. Participants are presented with negative visual feedback on their performance by the program (i.e., ‘incorrect’, ‘timeout’, and a comparison of individual performance with (fake) average performance), and negative verbal feedback by the experimenter (e.g., “Your performance is below of what we normally see, can you please try harder?”). The MIST has been utilised in numerous clinical and non-clinical studies and reliably increases subjective,
neurological and physiological indicators of stress (Geva, Pruessner, and Defrin, 2014; Hernaus et al., 2015; Mizrahi et al., 2014; Voellmin et al., 2015; Zschucke, Renneberg, Dimeo, Wüstenberg, and Ströhle, 2015). Participants are fully debriefed after the task is finished and no adverse effects have been reported.

5.2.2.2 Voice-simulation

Three 10 minutes audio materials were developed for the present study: a) negative simulated voices (e.g., “What a waste of space”), b) neutral simulated voices (e.g., “Today is the day”), and c) non-voice neutral sounds (i.e., the sound of water running). To ensure validity of the voice simulation, an initial longlist of negative and neutral voice comments was drawn from a) online first-person reports of voice content in service user forums, b) service user literature and c) reports from clinicians with expertise in working with psychosis patients. The final shortlist was established excluding comments that were performance- and task-specific, or too derogatory and/or potentially risky (e.g., commands of self-harm). Voice-tracks were identical in the number of statements, the number of first-person statements, as well as the frequency of words within the English language (assessed using Subtlex-UK; van Heuven, Mandera, Keuleers, and Brysbaert, 2014). The tracks were designed to deliver comments for 10min, with a total of 170 comments in each. The comments were read out by two male and two female volunteers who were instructed to maintain a neutral intonation to avoid confounding content with intonation. Time intervals between voices were matched for the negative and neutral tracks, as well as which speaker delivered the specific statement. The number of statements delivered by female and male voices was even. The non-voice control track consisted of a 10min recording of water streams. See Appendix II for a full breakdown of the voice-tracks.

5.2.2.3 Southampton Mindfulness Questionnaire

The Southampton Mindfulness Questionnaire (SMQ) is a 16-item self-report measure that assesses mindful awareness of distressing thoughts, images and voices (Chadwick et al., 2008).
For the present study, only mindfulness of voices was assessed. Items are scored on a 7-point Likert scale from 1-7, with total scores ranging from 16 to 112, and higher scores indicating greater state mindfulness. Its validity has been shown in both clinical and healthy samples (Chadwick et al., 2008). For the purpose of the present study, the phrasing “Usually when I experience distressing voices...” was replaced by “When I heard the voices in the experiment...” in order to assess retrospective assessment of mindful appraisals of voices. Cronbach’s α in the present study indicated good reliability (0.87).

5.2.2.4 Visual Analogue Stress Scale

An 8-item visual analogue scale (VAS; Appendix III) was created to assess subjective stress-reactivity before and after the task, ranging from 0cm to 16.5cm, with total scores ranging from 0 to 132 and higher scores indicating greater subjective stress levels. Participants were asked how stressed, anxious, angry, relaxed (reverse coded), threatened, embarrassed, socially judged and expecting of positive vs negative consequences they were, to reflect an array of possible stress responses. A Principal Component Analysis was carried out to determine whether the scale represented a latent factor indicative of a general subjective stress reaction, using VAS scores at post-MIST. The Kaiser-Meyer-Olkin measure was used to verify sampling adequacy (KMO =0.84) and Bartlett’s test of sphericity indicated sufficiently large correlations ($\chi^2$ (28) = 259.8, p < 0.001). Only one component had an eigenvalue over Kaiser’s criterion of 1, explaining 50.49% of the variance. Since no item had a coefficient below 0.5 (Field, 2014), all 8 items were included, with the lowest factor loading being 0.61. Cronbach’s α indicated good overall reliability (0.86).

5.2.2.5 Biological Control Variables

To investigate potential confounding variables that may lead to variation in salivary biomarker data, a questionnaire (Appendix IV) was created to control for biological factors that may impact on physiological stress-function. Items assessed included age (Holochwost et al., 2017; Skoluda
et al., 2017), gender (Kirschbaum, Kudielka, Gaab, Schommer, and Hellhammer, 1999), BMI (Skoluda et al., 2017), native language (for voice content), current medications, current medical diagnoses, time of last meal, time of last drink, time of last cigarette (if applicable; Skoluda et al., 2017), first day of last menstrual cycle (if applicable; Kirschbaum et al., 1999), strenuous exercise in the preceding 72 hours (h) (Bonato et al., 2017), stress exposure in the preceding 24h (Skoluda et al., 2017), and illicit substance use in the preceding 72h (Seibert et al., 2014). A composite score for menstrual cycle and oral contraceptives (progesterone) was created using stratification by follicular and luteal phase and gender, so that women in luteal phases and men were grouped, and women in follicular phases and oral contraceptive users were grouped. This is in line with previous research demonstrating the effect of these variables on salivary cortisol reactivity to psychosocial stress (Kirschbaum et al., 1999). Participants with substance use in the preceding 72h were excluded.

5.2.2.6 Cortisol and α-Amylase Measurements

Saliva was sampled using Salivettes (Rommelsdorf, Germany). All Salivettes were frozen at -20 °C in a secure laboratory freezer within 2 hours of collection. Participants were asked to gently chew the Salivettes for each collection, and were instructed not to touch samples with their hands. All samples were analysed at the StressLab (Trier, Germany) using ELISA-assays for cortisol and α-amylase, with an inter-assay variability coefficients of 5.2% and 3.0%, respectively.

5.2.3 Procedure

Participants were told that the aim of the study was to test the effects of auditory stimuli on cognitive abilities. Figure 5.1 summarises the procedure. Eligible participants completed an initial VAS and saliva sample, and were then invited to practice on the MIST (i.e., they completed equations without a time limit, and without the audio track) for 10min. All participants were instructed to use the keyboard with their non-dominant hand to increase difficulty. During the
actual trial, participants wore a headset with the headphone covering their left ear (with the experimenter sitting to their right) to present auditory stimuli. Auditory stimuli were block-randomised (www.sealedenvelope.com) so that there were 28 participants in each group, and organised by a collaborator so that the experimenter was blinded to individual conditions. Participants were asked not to comment on the content of the auditory stimuli during their performance to avoid unblinding the experimenter. Further, they received no instructions on a particular response style (e.g., mindfulness) to the auditory stimuli.

Participants were asked to complete the second VAS and saliva sample, and then started the MIST experimental condition for 10min whilst listening to the audio stimuli. Participants in all conditions were exposed to criticising negative social feedback by the experimenter, including questioning of their arithmetic abilities, their effort in the experiment, as well as warnings that they would be excluded if their performance did not improve. The experimenter did not respond to any queries made by the participants. Following completion of the MIST, participants were immediately asked to complete the third VAS and saliva sample. They were then fully debriefed about the true nature of the task, and participants in the two voice conditions completed the SMQ. Participants then completed the assessment of control variables, and three more VAS and saliva samples were taken in intervals of 15min.
Figure 5.1 – Flow diagram of experimental procedures
5.2.4 Statistical Analysis

Frequentist statistical analyses were carried out using SPSS for Windows (IBM Corp., 2015) and JASP (JASP Team, 2016) was used for Bayesian analysis to express likelihood of data supporting the hypotheses. A repeated-measures mixed 6 (sampling time points) X 3 (condition: negative voices; neutral voices; ambient sounds) ANCOVA was carried out on the total VAS scores, cortisol and α-amylase. Lower-order repeated-measures ANOVAs were used for post-hoc testing of condition-specific effects. To establish normal distribution of cortisol and α-amylase data, logarithmic transformations (log) were undertaken for all analyses. For all cortisol and α-amylase analyses, associations of dependent variables with potential covariates, including BMI, age, gender and menstrual cycle, were assessed and included as covariates if significant. For cortisol, bivariate correlations revealed current gender and menstrual cycle as potential covariates. For α-amylase, no potential covariates were identified. For tests for associations, the area under the curve with respect to the ground (AUCg), i.e., the total amount of biomarker secretion across all time points (Pruessner, Kirschbaum, Meinlschmid, and Hellhammer, 2003) was calculated as:

\[ AUC_g = \sum_{i=1}^{n-1} \frac{(m_{i+1} + m_i) \cdot t_i}{2} \]

With \( t_i \) denoting the time between measurements and \( m_i \) denoting biomarker values at individual measurement time points. Bivariate correlations with AUCg cortisol and α-amylase were utilised for associations with SMQ. It was planned to use PROCESS (2.16.3) for SPSS (Hayes, 2013) for moderation analyses should potential moderators be identified.

Normal distribution of data was checked by Q-Q plots, and Levene’s test confirmed homogeneity of variance between the three conditions. Non-normally distributed data was analysed using non-parametric methods. P-values below the two-tailed 0.05 threshold were accepted as
statistically significant. False Discovery Rate correction for multiple testing was applied to analyses with multiple post-hoc testing, and FDR-adjusted p-values are reported where indicated (Benjamini and Hochberg, 1995). Calculated effect sizes were converted to Cohen’s d to allow for comparison across effects. Effect size conversions were carried out using formulas commonly used in meta-analyses and research synthesis (Borenstein et al., 2009; Cooper et al., 2009; Fritz et al., 2012; Lipsey et al., 2001; Morris and DeShon, 2002). Bayes factors of 3 and above were interpreted as sufficient evidence for the alternative hypothesis, and Bayes factors of 1/3 and below as sufficient evidence for the null hypothesis (Kass and Raftery, 1995).

5.3 Results

5.3.1 Demographic Descriptives

One-way ANOVAs showed randomisation was successful, with no significant differences in age (F (2, 81) = .03, p = .97, d = 0.05, BF_{10} = .2), gender (F (2, 81) = 1.16, p = .32, d = 0.34, BF_{10} = .3), BMI (F (2, 81) = 1.4, p = 0.25, d = 0.37, BF_{10} = 0.3) or number of native English speakers (F (2, 81) = .96, p = .39, d = 0.31, BF_{10} = .2) between conditions. One-way ANOVA also confirmed that VAS scores did not differ between conditions at pre-MIST (F (2, 81) = .64, p = .85, d = 0.31, BF_{10} = .2), and neither did cortisol (F (2, 81) = 0.51, p = 0.51, d = 0.22, BF_{10} = 0.2) or α-amylase (F (2, 81) = 0.77, p = 0.47, d = 0.28, BF_{10} = 0.2). Demographics and questionnaire scores by condition are presented in Table 5.1. Two participants in the negative voices condition decided to abort the MIST after 8 minutes but nevertheless participated in the rest of the study and were therefore included in the analyses. Two participants in the negative voices condition accidentally unblinded the experimenter but were included as their data were not indicative of outliers.
Table 5.1 – Demographics, questionnaire scores and biomarker levels by condition (mean ± SD unless specified otherwise)

<table>
<thead>
<tr>
<th></th>
<th>NEG (n = 28)</th>
<th>NEU (n = 28)</th>
<th>AMB (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% female)</td>
<td>75.0%</td>
<td>82.1%</td>
<td>64.3%</td>
</tr>
<tr>
<td>Age (y)</td>
<td>25.9 ± 7.6</td>
<td>26.4 ± 8.5</td>
<td>26.0 ± 5.9</td>
</tr>
<tr>
<td>Native Language (% English)</td>
<td>64.3%</td>
<td>71.4%</td>
<td>53.6%</td>
</tr>
<tr>
<td>VAS Overall Delta*</td>
<td>5.5 ± 1.9</td>
<td>3.2 ± 1.7</td>
<td>3.9 ± 2.5</td>
</tr>
<tr>
<td>SMQ*</td>
<td>16.5 ± 3.5</td>
<td>20.5 ± 4.0</td>
<td>-</td>
</tr>
<tr>
<td>Cortisol AUCg (log)</td>
<td>5.5 ± 0.6</td>
<td>5.6 ± 0.6</td>
<td>5.7 ± 0.7</td>
</tr>
<tr>
<td>α-Amylase AUCg (log)</td>
<td>9.3 ± 0.8</td>
<td>9.4 ± 0.6</td>
<td>9.2 ± 0.6</td>
</tr>
</tbody>
</table>

Note: NEG – negative condition; NEU – neutral condition; AMB – ambient condition; VAS – Visual Analogue Scale; SMQ – Southampton Mindfulness Questionnaire; * - statistically significant difference between groups

5.3.2 Subjective Effects (VAS scores)

Sensitivity analyses using G*Power for Windows (Faul et al., 2007) indicated that the repeated-measures ANOVA analyses were powered to detect within-between group interactions at effect sizes of Cohen’s d = 0.26, at β = 0.8.

Mauchly’s Test of Sphericity was significant; therefore Greenhouse-Geisser statistic is reported. Repeated-measures ANOVA confirmed a significant effect of time point on VAS scores (F (2.5, 198.4) = 234.1, p < .001, d = 3.40, BF₁₀ = 9.5 x 10¹⁰⁸), and there was a significant interaction with condition (F (4.9, 198.4) = 4.8, p < .001, d = 0.70, BFₙₐ = 4308.0). Tests of between-groups effects showed no significant effect of group (F (2, 81) = 0.04, p = 0.961, d = 0.006, BF₁₀ = 0.05). As visual inspection suggested that the significant interaction arose from pre- to post-MIST, lower-order ANOVAs were carried out assessing only pre- to post-MIST VAS scores, using FDR-adjusted p-values to adjust for multiple comparisons. This showed significant group differences in VAS change (F (2, 83) = 9.7, p = .002, d = 0.98, BF₁₀ = 162.7), with significantly greater change in NEG compared to NEU (p = .002) and NEG compared to AMB (p = .01), but no differences between NEU and AMB (p = 0.41). VAS scores throughout the paradigm are showed in Figure 5.2. Mean
deltas from pre- to post-MIST for individual as well as total VAS scores are presented in Figure 5.3 to show change in stress levels from baseline by condition.

**Figure 5.2** – VAS scores by group by time point (mean ± SE)
5.3.3 Biomarker Effects

Mauchly’s Test of Sphericity was significant; therefore Greenhouse-Geisser statistic is reported. Repeated-measures ANCOVA controlling for gender and menstrual phase confirmed a significant effect of time point on cortisol levels ($F(1.9, 150.6) = 5.7$, $p = .0052$, $d = 1.87$, $BF_{10} = 2.7 \times 10^{15}$), but there was no significant interaction with condition ($F(3.8, 150.6) = 1.0$, $p = .41$, $d = 0.55$, $BF_{M} = 0.03$). No significant effect of group was found ($F(2, 79) = 0.46$, $p = 0.63$, $d = 0.02$, $BF_{10} = 0.2$). Repeated measures ANOVA also confirmed a significant effect of time point on α-amylase levels ($F(2.9, 233.4) = 23.0$, $p < .001$, $d = 1.73$, $BF_{10} = 3.8 \times 10^{13}$), but there was no significant interaction with condition ($F(5.8, 233.4) = 0.1$, $p = .71$, $d = 0.42$, $BF_{M} = 0.01$). No significant between-groups effect was found ($F(2, 80) = 0.32$, $p = 0.73$, $d = 0.02$, $BF_{10} = 0.3$). Cortisol and α-amylase scores throughout the paradigm are showed in Figures 5.4 and 5.5, respectively.
Figure 5.4 – Cortisol by group by time point (mean ± SE)

Figure 5.5 – α-Amylase by group by time point (mean ± SE)
5.3.4 Moderating Effects

Sensitivity analyses using G*Power for Windows (Faul et al., 2007) indicated that the correlation analyses were powered to detect associations at effect sizes of $r = 0.30$, at $\beta = 0.8$.

Bivariate correlation showed that SMQ scores were negatively associated with total VAS delta scores ($r = -.39$, $p = .003$, $d = 0.85$, $BF_{10} = 11.3$; Figure 5.6). However, as shown in Table 5.1, independent t-test revealed a significant effect of voice condition on SMQ scores ($t (54) = 3.92$, $p < .001$, $d = 1.06$, $BF_{10} = 99.8$), with significantly lower SMQ scores, indicating lower mindfulness, in the negative voice condition ($M = 66.18$, $SD = 14.11$) compared with the neutral voice condition ($M = 81.96$, $SD = 15.97$). Post-hoc analyses further showed that the negative association of SMQ scores with VAS deltas was significant in the negative ($r = .43$, $p = .03$, $d = 0.95$, $BF_{10} = 1.9$) but not in the neutral ($r = .05$, $p = .81$, $d = 0.10$, $BF_{10} = 0.24$) voice condition, although Fisher’s r-to-z suggests the difference in correlations not to be significant ($p = .15$). Due to the lack of independence between SMQ scores and condition it was not possible to carry out moderation analyses.
Further bivariate correlations showed no significant association between SMQ scores and either log$_n$ AUC$_g$ cortisol ($r = -0.23, \ p = 0.08, \ d = 0.47, BF_{10} = 0.7$) or log$_n$ AUC$_g$ α-amylase ($r = 0.03, \ p = 0.85, \ d = 0.06, BF_{10} = 0.2$). Due to the lack of main effect of condition on cortisol or α-amylase it was not possible to carry out any moderation analyses.

5.4 Discussion

5.4.1 Findings

Our main finding was that, as predicted, experiencing negative simulated voices exacerbated the subjective stress response compared with neutral voices and ambient sounds, with a large effect size. The effect of neutral voices and ambient sounds on subjective stress-reactivity did not differ, indicating that the effect is specific to negative voices rather than voices per se. Our
findings thus indicate that there is a large effect of negative voice content on the subjective stress response, which in turn may drive differential stress-reactivity in clinical voice-hearers. However, this finding was not mirrored in cortisol or α-amylase levels: differences across time points indicated that the MIST affected physiological stress response, but there were no differences across conditions. A recent study demonstrated that pharmacological suppression of both HPA- and ANS-activity via dexamethasone and propranolol does not alter the subjective emotional response to psychosocial stress in healthy individuals (Ali, Nitschke, Cooperman, and Pruessner, 2017), suggesting that psychological and physiological stress levels can vary independently. Thus, it is possible that our findings indicate that voice-content is unrelated to potential differences in HPA- and ANS-function of HVHs and CVHs, despite potential subjective stress differences.

We also found that more mindful appraisals of voices were associated with lower subjective stress-reactivity. Interestingly, this was only the case in the negative voice condition, but not the neutral voice condition. Thus, mindfulness-based coping strategies may be a useful strategy to ameliorate distress associated with negative voices; however, negative voice content was also associated with lower state mindfulness after stress exposure. This finding adds to evidence from trials of mindfulness for clinical voice-hearers, which found evidence of reduced voice distress following therapy (Chadwick et al., 2016, 2009; López-Navarro et al., 2015; Shawyer et al., 2007). However, the lack of main effect of condition on cortisol or α-amylase made it impossible to test for a moderation effect.

5.4.2 Strengths and Limitations

We took great care in developing the simulated voices, consulting clinicians and voice-hearers on both the content and delivery of the voices in an iterative process. A strength of the present study is the development of simulated voices of negative and neutral content for use in research that have face validity and evoke differing levels of distress. Whilst previous research has
suggested simulated hallucinations are seen as realistic depictions by psychosis patients (Banks et al., 2004), to our knowledge this is the first research to show differences in affective reactions depending on voice content. Nevertheless, it is important not to assume generalisation of findings from research using simulated voices to the experience of clinical voice-hearers. Several aspects of AVHs, such as their interactive nature and personalised comments, are difficult to simulate, and there were ethical limits on how derogatory the content could be. Also, future research is needed to determine the impact of the simulated voices in other contexts, and not only under conditions of environmental stress.

The use of randomisation to control for individual differences in prior stress exposure and stress-reactivity, and the blinding of the experimenter to condition, further add to the strength of the present study. Similarly, Bayesian models were used to successfully confirm frequentist statistics in the present study, thereby increasing confidence in the results. A marked limitation of the present study is that it remains unclear as to whether the lack of biomarker findings is related to an independence of these markers from voice-content (and subjective stress levels) in actual voice-hearers as well. Alternatively, HPA- and ANS-parameters may not be sufficiently sensitive to reveal subtle differences in stress levels, which are better captured by subjective reports. Further, it was not anticipated that voice content conditions would influence mindfulness scores, which meant it was not possible to assess moderation effects. Whilst mindfulness regarding voices may have been of more relevance to the specific research question, trait mindfulness or state assessment before experimental exposure may have been more appropriate measures to test the hypothesis.

5.4.3 Implications and Future Directions

The present findings suggest that negative voice content may be a driving factor in the subjective stress-reactivity and distress of clinical voice-hearers. Future research should investigate the predictive value of negative voice content in transition rates of at-risk populations, rather than
merely the presence of voices, potentially aiding early identification of at-risk individuals and allowing for early intervention. The present subjective stress findings may have further implications for understanding the development and maintenance of psychotic disorders. According to a recent stress feedback model proposed by Howes and colleagues (2016), stress exposure may exacerbate dopaminergic dysregulation, which then leads to greater levels of delusional ideation and aberrant salience, increasing need for care and distress and thus maintaining this cycle. Increased stress levels due to negative voice content may putatively contribute to dopamine dysfunction and the formation of delusional beliefs. In line with this, the effect of the present paradigm on delusional ideation, e.g., state paranoia, should be assessed in future research. Further, whilst the present study found evidence that mindful appraisal of voices is associated with attenuated subjective stress-reactivity, future research should address experimentally whether purposefully employed mindful response styles to voices also attenuate stress-reactivity, or whether mindful response styles are simply more prevalent in individuals with greater stress resilience.

5.4.4 Conclusions

Participants exposed to voices with negative content showed an increased subjective stress reaction to a psychosocial stressor compared with those who were exposed to voices with neutral content or an ambient sounds condition. This effect was moderated by mindful appraisals of voices, but negative voice content itself reduced mindful appraisals. No significant effect of voice condition on either HPA- or ANS-function were observed. The present study adds support to the emergence of mindfulness-based therapies for negative, distressing voices, and underscores the importance of addressing both content of voices and appraisals in psychological therapies for voices.
Chapter 6 – Psychophysiological Stress-Function in Clinical and Healthy Voice-hearers

6.1 Introduction

Several key conclusions can be drawn from the evidence presented in Chapters 2 and 3. First, there is considerable evidence to suggest that psychosis is closely linked with stress and stress-function, and that traumatic stress exposure is directly related to AVHs. Childhood sexual and physical abuse are highly prevalent in psychosis patients, and there is evidence to suggest that such experiences are particularly linked to auditory verbal hallucinations and other positive symptoms (Bentall et al., 2012; Hardy et al., 2016; Read et al., 2005; Shevlin et al., 2007). Psychosis patients are more likely to appraise events in daily life as stressful (Myin-Germeys et al., 2001), daily life stressors are positively associated with intensity of psychotic experiences (Myin-Germeys et al., 2005) and elevated stress-sensitivity to daily events as well as increased threat anticipation are associated with greater rates of psychotic experiences (Reininghaus et al., 2016). Evidence from self-report, experimental, and neuroimaging studies strongly suggests increased threat perception in psychosis and need for care (Reininghaus et al., 2016; Underwood et al., 2016). Similarly, physiological stress-function is perturbed in psychosis. In the autonomic nervous system (ANS), the sympathetic (SNS) branch is unaltered in psychosis, whereas activity of the parasympathetic (PNS) branch is dampened, establishing an imbalance in ANS activity (Montaquila et al., 2015). In addition to markers such as heart rate variability and respiratory rates, the salivary marker α-amylase has been investigated as a potential measure of ANS balance in psychosis, with two reports of increased levels in psychosis (Ieda et al., 2014; Inagaki et al., 2010). Further, there is evidence for altered hypothalamic-pituitary-adrenal (HPA) function in psychosis. Baseline HPA activity appears to be increased in patients with psychosis (Bradley and Dinan, 2010; Pruessner, Cullen, Aas, and Walker, 2017) and there is evidence of a blunted response to psychosocial stress (Ciufolini et al., 2014). Further, morning cortisol levels
are elevated (Girshkin et al., 2014), and negative feedback in the HPA axis, as measured via cortisol response to dexamethasone, a selective agonist of the glucocorticoid receptor (GR), is diminished (Bradley and Dinan, 2010). Evidence further suggests that one of the primary mechanisms regulating GR-availability, the chaperone protein FKBP5 that binds cytosolic GR, is involved in a genetic interaction with childhood trauma in the emergence of psychotic symptoms and HPA dysregulation (Collip et al., 2013a). Given the strong link between trauma exposure and the emergence of AVHs, it is warranted to also investigate the role that subjective and physiological stress-function may play in the impact of voice-hearing.

Second, the current literature on HVH suggests that their AVHs are closely related to those of CVHs, but do not have the same distressing impact. The ability of an individual to respond to stress in an adaptive manner and overcome stress exposure may be a key variable when trying to understand why some individuals who hear voices suffer distress and present with need for care, whilst others do not. To address this question, the present study set out to investigate the role of physiological stress-function in leading to need for care in voice-hearers. A cross-sectional design was used comparing CVHs, HVHs and healthy controls with no AVHs (HCs). In line with recent suggestions of the Research Domain Criteria framework (Insel et al., 2010), recruitment of CVHs for the present study was symptom-specific and transdiagnostic, rather than guided by diagnostic criteria. That is, for participants to be included as CVHs, they had to a) experience AVHs and b) have received mental healthcare specific to psychotic experiences. That means that in addition to the classical diagnoses AVHs are usually considered a part of, i.e., schizophrenia and schizophreniform disorders, the present study also allowed for the inclusion of research participants diagnosed with other disorders, such as depressive disorder, post-traumatic stress disorder, and bipolar disorder. Therefore, to our knowledge this is also the first research to investigate physiological stress-function specifically in relation to CVHs, rather than in schizophrenia populations where AVHs may or may not be present.
Several experimental and natural stress parameters were chosen to allow for a comprehensive assessment of stress-function. To investigate baseline HPA and ANS function, salivary cortisol and α-amylase were measured three times (Awakening, 3pm and 8pm) over the course of one day. To assess GR-function and negative feedback capacity of the HPA axis, the Dexamethasone Suppression Test (DST; Cole, Kim, Kalman, and Spencer, 2000) was chosen, with three salivary cortisol measurements (Awakening, 3pm and 8pm) over the course of one day following 1mg dexamethasone administration. To investigate acute reactivity of the HPA axis and the ANS to a psychobiological stress induction, the Socially-Evaluative Cold Pressor Test (SECPT; Schwabe, Haddad, and Schachinger, 2008) with salivary assessment of cortisol and α-amylase was chosen, as well as subjective reactivity to the stressor and anticipatory stress appraisal. In order to characterise the study populations, the study included measures of AVH phenomenology, anomalous perceptual experiences, beliefs about voices, drug use, trait mindfulness, symptoms of mood disorder as well as perceived life stress.

6.1.1 Research Questions and Hypotheses

6.1.1.1 Research Questions

1. Do CVHs, HVHs and HCs differ in their baseline HPA and ANS function, as assessed via salivary cortisol and α-amylase levels at three time points (i.e., total diurnal cortisol) over one day and at awakening?

2. Do CVHs, HVHs and HCs differ in their GR-mediated negative feedback, assessed via cortisol response to the DST?

3. Do CVHs, HVHs and HCs differ in their subjective, cortisol and α-amylase response to psychobiological stress, induced by the SECPT, as well as their anticipatory stress appraisal of the SECPT?
6.1.1.2 Hypothesis 1 – Baseline Stress Function

CVHs will have higher cortisol levels at the awakening than both HVHs and HCs. CVHs will show elevated overall cortisol and α-amylase levels compared with HVHs and HCs over the total (Awakening, 3pm and 8pm) of the day. HVHs will not differ from HCs on either parameter.

6.1.1.3 Hypothesis 2 – Dexamethasone Suppression Test

CVHs will show less cortisol suppression in response to dexamethasone challenge than HVHs, indicative of impaired function of the GR and HPA auto-regulation. HVHs will not differ from HCs.

6.1.1.4 Hypothesis 3 – Socially-Evaluative Cold Pressor Test

CVHs will show an exacerbated salivary α-amylase reaction in the context of a blunted cortisol response to the SECPT, compared to HVHs and HCs. Overall cortisol levels will be higher in CVHs compared to HVHs and HCs. CVHs will show increased anticipatory stress appraisal before exposure and have higher subjective stress levels throughout the paradigm, including greater overall levels and diminished recovery. HVHs will not differ from HCs on any parameters.

6.2 Methods

6.2.1 Participants

6.2.1.1 Sample Selection

Three groups of participants were recruited:

1. 20 patients with auditory verbal hallucinations (AVH) from two services in the South London and Maudsley (SLaM) NHS Foundation Trust Psychosis Clinical Academic Group (CAG) (i.e. CVHs)
2. 25 voice-hearers with no need for care from community samples and specialist organisations (i.e. HVHs)

3. 23 healthy non-voice-hearing controls from the general population (i.e. HCs).

### 6.2.1.2 Inclusion and Exclusion Criteria

All participant groups had to meet the exclusion and inclusion criteria listed in Table 6.1.

<table>
<thead>
<tr>
<th>Table 6.1 – Inclusion and exclusion criteria for all groups</th>
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</thead>
<tbody>
<tr>
<td><strong>Inclusion Criteria</strong></td>
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<td><strong>Exclusion Criteria</strong></td>
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English language abilities were decided to be essential for participation (Exclusion criterion 2). Additional selection criteria excluded individuals for whom dexamethasone may be contraindicated (Exclusion criteria 3, 5 and 6). In line with findings by Goldman and colleagues (2007), individuals with polydipsia (excessive water consumption, assessed by asking about excessive thirst or urination) were excluded as this may confound accurate assessment of HPA
parameters in psychosis patients (Exclusion criterion 7). Raynaud’s phenomenon, which is associated with excessively reduced blood flow in response to cold or stress exposure due to vasospasm, was a further exclusion criterion (4) for the SECPT.

6.2.1.2.1 Clinical Voice-Hearers

For CVHs to be included in the present study they had to meet the additional following criteria in Table 6.2.

Table 6.2 – Inclusion and exclusion criteria for CVHs

| Inclusion Criteria | 1. Current auditory verbal hallucinations (as indicated by a score of 1 (weekly) or above on the PSYRATS frequency item) in absence of drug use and in clear consciousness |
|                   | 2. They are currently using secondary mental health services in relation to psychotic experiences |

| Exclusion Criteria | 1. Too agitated or distressed to take part (i.e., acutely unwell, as informed by care coordinator or assessed to be so by interviewer) |
|                   | 2. Drug-induced or organic psychosis. |

Drug induced or organic psychoses were excluded, as these may have fundamentally different aetiologies (Exclusion criterion 2).

6.2.1.2.2 Healthy Voice-Hearers

For HVHs to be included in the present study they had to meet the additional following criteria in Table 6.3.
### Table 6.3 – Inclusion and exclusion criteria for HVHs

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>1. Presence of auditory hallucinations for at least 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Current auditory verbal hallucinations (as indicated by a score of 1 or above on the PSYRATS frequency item) in absence of drug use and in clear consciousness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
<th>1. They have sought help (either themselves, or someone on their behalf) from mental health services in relation to their psychotic experiences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. They have received secondary care for any mental health issue</td>
</tr>
<tr>
<td></td>
<td>3. A clinical judgement is made that the participant is in need of care (e.g., reporting of distress or significant mental health difficulties)</td>
</tr>
</tbody>
</table>

Selection criteria assessing need for care in potential HVHs (Exclusion criteria 1-3) were made in line with previous studies on psychotic experiences in healthy individuals (Peters et al., 2016; Ward et al., 2014). To further ensure that AVHs were persistent in potential participants and to avoid recruiting individuals in a potential prodromal state, AVH had to have been occurring for at least 5 years in the absence of need for care (Inclusion criterion 1).

### 6.2.1.2.3 Healthy Controls

For HCs to be included in the present study they had to meet the additional following criteria in Table 6.4.

### Table 6.4 – Exclusion criteria for HCs

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
<th>1. Current or past presence of auditory verbal hallucinations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. They have sought help (either themselves, or someone on their behalf) from mental health services in relation to any psychotic experience</td>
</tr>
<tr>
<td></td>
<td>3. They have received secondary care for any mental health issue</td>
</tr>
</tbody>
</table>
Healthy controls had to fulfill the same criteria for absence of help-seeking as HVHs, with the additional exclusion criterion of previous experience of AVHs.

6.2.1.3 Recruitment

Recruitment of CVHs was through two primary SLaM sources: a) the PICuP (Psychological Interventions Clinic for outpatients with Psychosis) research register, a database of potential research volunteers who had been previously assessed and/or treated by the team; and b) referrals by the Treatment Review and Assistance Team (TREAT), a specialist service for patients with on-going psychotic symptoms (Beck et al., 2014). All recruited CVHs were outpatients.

Recruitment of HVHs primarily relied on the UNIQUE (‘UNusual experIences enQUiry’) study research register, containing contact details for potential volunteers who have reported psychotic experiences in previous research studies (Peters et al., 2016; Ward et al., 2014). Additionally, the present project utilised opportunity sampling, including research advertisement through spiritual groups (e.g., Society for Psychical Research), GumTree (www.gumtree.com), as well as direct contacting of individuals advertising themselves as ‘clairaudient’ mediums or spiritual practitioners, consistent with the approaches used in previous studies recruiting this population (Underwood et al, 2016; Peters et al., 2016).

HCs were recruited through opportunity sampling, including adverts in the KCL internal research recruitment newsletters, GumTree (www.gumtree.com), Experimatch (www.experimatch.com; a participant recruitment website formerly provided by University College London), and through a snowballing approach (i.e., asking participants to forward information sheets to friends and family).
6.2.2 Materials

6.2.2.1 Experimental Measures

6.2.2.1.1 Dexamethasone Suppression Test

The DST uses the synthetic glucocorticoid dexamethasone, a selective agonist for the GR, to assess negative feedback capacity in the HPA axis. The present study utilised dexamethasone (1mg) in oral pill form, which is a commonly used dose in the DST and recommended by the American Endocrine Society (Nieman et al., 2008). The salivary cortisol level was measured at three time-points (awakening, 3pm and 8pm) on a baseline day to establish normative HPA function. This procedure was carried out by participants at home, using written instructions and phone support if needed. Participants then self-administered the 1mg dexamethasone in the evening, and salivary cortisol levels were measured again over the following day. Post-DST cortisol levels were used to assess whether dexamethasone led to suppression of cortisol release and thus whether negative feedback capacity in the HPA axis is normative.

Further, time of awakening was used for the morning sample, rather than asking participants to set an alarm for a specific time. This was decided to allow for individual variation in awakening times and diurnal activity patterns. To assess potential differences in awakening between groups, participants were asked to record the time of awakening on both days. The dexamethasone in the present study was dispensed by the Maudsley Pharmacy and prescribed by the study physician. Effects of oral dexamethasone induced cortisol suppression last for approximately 2-3 days (Cassidy et al., 2000).

6.2.2.1.2 Socially Evaluated Cold Pressor Test

The SECPT is a psychobiological stress task that is designed to elicit an acute stress response. It is based on the Cold Pressor Test, where an extremity, typically a hand, is exposed to cold, painful stimuli such as ice water or cool packs in order to elicit a stress response. Schwabe and
colleagues (Schwabe, Haddad, and Schachinger, 2008) refined the classic paradigm by including a social component to exacerbate the HPA response. In the SECPT participants are additionally informed that their facial expressions will be filmed during the task, and they are asked to maintain eye contact with a camera set up in front of them, and the experimenter sits adjacent to them and pretends to take notes. Implementing these modifications has been shown to produce a greater HPA response than the ‘classic’ Cold Pressor Task (Schwabe, Haddad, and Schachinger, 2008).

Conventional freezer ice packs were used to cool down the water, and temperature was measured using a digital thermometer to ensure that all participants were exposed to temperatures between 0-3°C. Maximum exposure was set at 3min, after which participants were asked to remove their hand from the water if they had not already done so. Saliva and subjective stress was measured at two time points before exposure (-10min and 0min) and at 5 time points following exposure (0min, +15min, +30min, +45min and +60min). During the rest phase, all participants were presented with a 60-min nature documentary (BBC Natural History Unit, 2011) to provide a controlled stimulus. Whilst research studies frequently employ the use of magazines for such waiting periods (Birkett, 2011), it was decided that a nature documentary would a) not lead to exposure to differential stimuli, i.e., individual articles, b) not pose an additional stressor for individuals with impaired reading abilities and c) would be less stressful than many news articles. The chosen documentary was age appropriate for children as young as six, to ensure that potentially stressful imagery (e.g., animals hunting) was kept to a low level.

6.2.2.1.3 Saliva Samples

Salivary cortisol and α-amylase levels were measured using Salivettes (Rommelsdorf, Germany). All Salivettes were frozen at -20 °C in a secure laboratory freezer. Freezing occurred within 2 hours of collection for all SECPT samples, and participants were instructed to freeze samples taken at home immediately after taking them. Participants were asked to gently chew the
Salivettes for each collection, and were instructed not to touch samples with their hands. All samples were analysed at the ViaPath lab at King’s College Hospital, using enzyme linked assay by Salimetrics. Inter-assay coefficients of variations were 7.1% for cortisol and 6.3% for α-amylase. All saliva samples obtained in the SECPT were assessed for cortisol and α-amylase content, as were samples taken on the baseline day of the DST. Samples taken following dexamethasone administration were assessed for cortisol only.

6.2.2.2 Questionnaire Measures

6.2.2.2.1 Psychotic Symptoms Rating Scale – AVH

The Psychotic Symptoms Rating Scale for Auditory Verbal Hallucinations (PSYRATS-AVHs) is a scale to assess dimensions of AVHs (Haddock, McCarron, Tarrier, and Faragher, 1999). It is administered in a semi-structured interview where 11 items are scored on a 5-point Likert scale (0-4). In line with Woodward and colleagues’ (2014) recent cluster analysis, a four-factor structure comprising distress (negative content, distress and control), frequency (frequency, duration and disruption), attribution (location and beliefs about origin) and loudness was utilised. The PSYRATS is a frequently used assessment tool that has repeatedly demonstrated validity and reliability in clinical and non-clinical voice-hearer populations (Daalman, et al., 2011a; Diederen et al., 2012; Haddock et al., 1999; Sommer et al., 2010a; Woodward et al., 2014). The PSYRATS was administered to voice-hearers only. In the present study, an item was included to record age of onset of AVHs.

6.2.2.2.2 Cardiff Anomalous Perceptions Scale

The Cardiff Anomalous Perceptions Scale (CAPS) is a self-report scale that measures the frequency, intrusiveness and distress of anomalous perceptual experiences that occur in a wakeful state, and in the absence of psychotropic medication or intoxication (Bell, Halligan, and Ellis, 2006). It contains 32 items, relating to psychotic experiences (e.g., hearing voices),
temporal lobe epilepsy symptoms (e.g., altered time perception), and chemosensation (e.g., olfactory hallucinations). The present study utilised the overall score (i.e., items endorsed), and the subscale totals for frequency, intrusiveness and distress of experiences. Each item is endorsed with a binary choice (yes/no), and then the frequency, intrusiveness and distress of each item is rated on a 5-point Likert scale from 1-5. This produces 4 scores, firstly the total number of items endorsed (total range 0-32), and then total frequency, intrusiveness and distress scores (total range for each 0-160), with higher scores reflecting greater endorsement. To ensure appropriate weighting, frequency, intrusiveness and distress scores were calculated as the sum of item scores divided by the number of items endorsed. It has demonstrated good reliability and validity in both clinical and non-clinical samples (Bell et al., 2006; Bell, Halligan, and Ellis, 2008; Bell, Halligan, Pugh, and Freeman, 2011). In the present study, the subscales for total score (Cronbach’s α = .93), total frequency (Cronbach’s α = .95), total intrusiveness (Cronbach’s α = .95) and total distress (Cronbach’s α = .95) all showed excellent reliability.

6.2.2.2.3 Beliefs About Voices Questionnaire

The Beliefs About Voices Questionnaire – Revised (BAVQ-R; Chadwick, Lees, and Birchwood, 2000) is a 30-item scale that measures beliefs about AVHs, as well as reactions to AVHs. Items are scored on a 4-point Likert scale (1-4). Beliefs are measured on three subscales each consisting of six items with scores ranging from 6-20, including beliefs of malevolence, benevolence and omnipotence, and reactions to AVHs (resistance and engagement, both emotionally and behaviourally) are measured on two subscales with nine and 8 items with scores ranging from 9-36 and 8-32, respectively. Higher scores reflect greater endorsement of individual subscales. Validity and reliability of the BAVQ-R has been demonstrated in both clinical and non-clinical voice-hearer populations (Andrew et al., 2008; Chadwick et al., 2000). In the present study, all subscales were found to be reliable: Malevolence (Cronbach’s α = .94), Benevolence (Cronbach’s α = .93), Omnipotence (Cronbach’s α = .76), Resistance (Cronbach’s α
=.95), and Engagement (Cronbach’s α = .96). The BAVQ-R was administered to voice-hearers only.

6.2.2.2.4 Voice Power Differential Scale

The Voice Power Differential Scale (VPDS) is a self-report measure consisting of six items to measure perceived power of the voice and voice-hearer (Birchwood et al., 2000). All items are bipolar in nature, i.e., they assess whether the voice or the voice-hearer is more powerful in relation to the other, rated on seven constructs (i.e., power, knowledge, superiority, strength, confidence, respectfulness, and ability to inflict harm). Each item is measured on a 5-point Likert scale (1-5; total range 6-30), with higher scores indicating greater voice power. The VPDS has demonstrated validity and reliability in CVH populations (Birchwood et al., 2000, 2004, 2014). Fifty-six percent of healthy voice-hearers reported being unable to answer the item regarding ability to inflict harm. Thus, the total scale was calculated on the basis of the remaining six items, and the harm item is reported separately. Cronbach’s α in the present study indicated good reliability for the six-item scale (Cronbach’s α = .83). The VPDS was administered to voice-hearers only.

6.2.2.2.5 Depression Anxiety and Stress Scale

The Depression Anxiety and Stress Scale (DASS) is a 42-item self-report instrument that assesses symptoms of depression, anxiety and stress in the preceding week (Lovibond and Lovibond, 1995). Its validity has been established in clinical as well as healthy samples (Crawford and Henry, 2003; Lovibond and Lovibond, 1995). The scale has three subscales covering symptoms of depression, anxiety and stress, each containing 14 items. Items are scored on a 4-point Likert scale from 0-3, with total subscale scores ranging from 0 to 42 and higher scores indicating greater symptoms for each individual subscale. Cronbach’s α in the present study indicated
reliability of the total score (Cronbach’s α = .98), as well as the depression (Cronbach’s α = .97), anxiety (Cronbach’s α = .91) and stress (Cronbach’s α = .94) subscales.

6.2.2.6 Five Facet Mindfulness Questionnaire

The Five Facet Mindfulness Questionnaire (FFMQ) is a 39-item self-report measure that assesses trait mindfulness (Baer, Smith, Hopkins, Krietemeyer, and Toney, 2006). Items are scored on a 5-point Likert scale from 1-5, with total scores ranging from 39 to 195, and higher scores indicating greater trait mindfulness. Only the total score was used in the present study. Previous studies have demonstrated good validity for the questionnaire (Baer et al., 2008; Bohlmeijer, ten Klooster, Fledderus, Veehof, and Baer, 2011). The present study found good reliability for the total score (Cronbach’s α = .81).

6.2.2.7 Stressful Life Events Questionnaire

The Stressful Life Events Questionnaire (SLESQ) is a 13-item assessment for lifetime exposure to stressful events that is administered as a semi-structured interview (Goodman, Corcoran, Turner, Yuan, and Green, 1998; Green, Chung, Daroowalla, Kaltman, and DeBenedictis, 2006). Items cover life-threatening events and exposure to physical, emotional and sexual abuse, as well as witnessing of such events. For each event, age of exposure, as well as specific details such as frequency and duration are recorded. For the present study, several scales were constructed, including total number of items endorsed (range 0-13), total number of sexual trauma exposure and total number of physical trauma exposure (each based on frequency item; both range 0-8).

6.2.2.8 Stress Appraisal Measure

To measure subjective anticipatory stress appraisal several subscales (Threat; Centrality; Uncontrollability) of the Stress Appraisal Measure (SAM; Peacock and Wong, 1990) were used,
combining how threatening, central (i.e., perceived as important to oneself) and uncontrollable the task was anticipated to be. The 12 selected items were scored on a 5-point Likert scale from 1-5, with total scores ranging from 5 to 60, and higher scores indicating greater anticipatory stress appraisal. The subscales have shown good validity (Peacock and Wong, 1990). The 12-item scale utilised here was found to be reliable in the present study (Cronbach’s α = .90).

6.2.2.9 Visual Analogue Scales

A 9-item visual analogue scale (VAS; Appendix VI) was created to assess subjective stress-reactivity, ranging from 0cm to 16.5cm (due to size of the scales on printed paper), with total scores ranging from 0 to 16 (one point for each centimetre interval) and higher scores indicating greater subjective stress levels. Participants were asked how stressed, in pain, anxious, angry, relaxed (reverse coded), threatened, embarrassed, socially judged and expecting of positive vs negative consequences they were, to reflect an array of possible stress responses to the SECPT. A Principal Component Analysis was carried out to determine whether the scale represented a latent factor indicative of a general subjective stress reaction, using VAS scores at baseline. The Kaiser-Meyer-Olkin measure was used to verify sampling adequacy. This showed KMO = .82 and Bartlett’s test of sphericity was significant ($\chi^2 (36) = 289.2, p < .001$). Three components had an eigenvalue over Kaiser’s criterion of 1, explaining 72.5% of the variance. A one factor structure was most appropriate (Eigenvalue = 4.44). It was decided to suppress items with coefficients below 0.5 (Field, 2014), leading to exclusion of one item (expecting positive vs negative consequences), with the lowest factor loading being .53. Cronbach’s α indicated the scale to be reliable (.85).

6.2.2.10 Drug Use

To assess use of recreational substances, a questionnaire was created to assess lifetime and current use of alcohol, tobacco, cannabis and amphetamines (including cocaine, crack-cocaine
methamphetamine, and 3,4-methylenedioxy-methamphetamine (MDMA)). For each class of drugs, frequency of use was recorded (if not current, then average at the time), current use and age of first exposure was assessed.

6.2.2.2.11 Demographics

A demographics questionnaire was created to assess age, gender, ethnicity, living status, relationship status, employment status, level of achieved education and native language of participants.

6.2.2.2.12 Biological Control Variables

To investigate potential confounding variables that may lead to variation in salivary biomarker data, a questionnaire was created to control for biological factors that may impact on physiological stress-function. Items assessed included age (Holochwost et al., 2017; Skoluda et al., 2017), gender (Kirschbaum et al., 1999), BMI (Skoluda et al., 2017), current medications, current medical diagnoses, time of last meal, time of last drink, time of last cigarette (if applicable; Skoluda et al., 2017), first day of last menstrual cycle (if applicable; Kirschbaum et al., 1999), strenuous exercise in the preceding 72h (Bonato et al., 2017), stress exposure in the preceding 24h (Skoluda et al., 2017), and illicit substance use in the preceding 72h (Seibert et al., 2014). A composite score for menstrual cycle and oral contraceptives (progesterone) was created using stratification by follicular and luteal phase and gender, so that women in luteal phases and men were grouped, and women in follicular phases and oral contraceptive users were grouped. This is in line with previous research demonstrating the effect of these variables on salivary cortisol reactivity to psychosocial stress (Kirschbaum et al., 1999).
6.2.3 Procedure

6.2.3.1 Recruitment

The study was carried out between November 2015 and February 2017. Potential participants were identified through research registers, opportunity or through care coordinators/nurses who asked potential participants if they would be happy to be contacted by the research team. All screenings were carried out by the research student. Once identified for potential eligibility for the project, participants were given an information sheet (see Appendix VII), informed about aims, methods and risks of the study and possible concerns, their rights as participants and what their participation entailed was discussed. Depending on the participants’ preference this was possible on the phone or face to face. Participants had at least 2 days to consider their participation before consenting.

If participants expressed their interest to participate, capacity to consent was assessed following standard procedures to determine capacity (Owen et al., 2013), consent was obtained and eligibility was assessed using inclusion/exclusion criteria. Again, this was possible on the phone or face to face depending on the participants’ preference. A study doctor was available for consultation on those issues if appropriate; in the case of uncertainty about previous, relevant medical diagnoses of e.g. endocrine disorders, participants were excluded. If the research student believed capacity was lacking or that understanding of the study and the procedures was not sufficient, participants were not included in the study. Participants were considered enrolled in the study once consented and verified eligible for inclusion. A record was held of those eligibility checks on a Clinical Research Form, which also documented completion of procedures by individual participants and any adverse events. Study procedures are presented in Figure 6.1.
6.2.3.2 Day 1 Assessment

At the first assessment, the study doctor screened all participants and, if necessary, carried out pregnancy testing. Participants then completed the questionnaire battery (in order: demographics; drug use; PSYRATS; CAPS; BAVQ-R; VPDS; SLESQ; DASS; FFMQ) with the research student. The procedures for the dexamethasone test were discussed in detail, and the research student ensured that participants understood those procedures by asking them to explain the procedure back to him. Participants further received a comprehensive flowchart (see Appendix VIII) detailing their participation and the procedures, as well as an information sheet about the dexamethasone suppression test and saliva sampling procedures (see Appendix V). Participants received 1mg of dexamethasone and 6 oral sorbettes, as well as full instructions for the sampling procedure. These instructions detailed the dexamethasone self-administration (Appendix V), saliva sampling and storage, as well as subsequent transportation, for which a padded envelope and sealable bags were provided.

6.2.3.3 Dexamethasone Administration and Saliva Sampling

Participants followed the saliva sampling procedures over two days at their home. All participants were offered reminder phone calls for the preceding day and the two sampling days to ensure compliance, acceptability and understanding and, if necessary, the procedure was explained again in more detail. On the first day, participants obtained one saliva sample upon awakening, another sample at 3pm, and a final sample in the evening at 8pm. Participants then took the 1mg dose of dexamethasone at 11pm, and repeated the collection of saliva samples upon awakening, 3pm and at 8pm of the following day. They were asked to store saliva samples in a provided bag in their fridge or freezer, and were scheduled for the second assessment at least 7 days following dexamethasone administration to avoid any carry-over effects (effects of oral dexamethasone induced cortisol suppression may last for approximately 2-3 days).
Participants who did not wish to receive reminder phone calls were contacted following the dexamethasone administration to ensure no adverse side-effects occurred.

### 6.2.3.4 Day 2 Assessment

On Day 2, participants brought their saliva samples and were again asked about any difficulties or subjective effects of dexamethasone. Participants then completed the Socially Evaluated Cold Pressor Task (SECPT). The protocol for the SECPT in the present study was as follows: at baseline, a saliva sample, subjective stress (VAS) as well as threat appraisal (SAM) measures (e.g., how stressful they anticipate the task to be; how well they think they will cope with the task) were taken. Then, 10min after the baseline time point, participants completed a second VAS and saliva sample, and were asked to immerse their hand up to and including the wrist in ice water, and keep their hand submersed for as long as possible. Participants were instructed to maintain eye contact with a camera placed in front of them, under the pretence that this was to analyse facial expressions. Additionally, participants were observed by the experimenter the whole time, who also took notes. Participants who still had their hand submersed after 3min were asked to remove it at that point. A record of the time their hand was submersed was taken for each participant. Upon completion, the third saliva sample and VAS score were obtained. Over the remaining 60min, during which participants had the opportunity to rest whilst watch a nature documentary, saliva and subjective stress (VAS) were measured every 15min.

Following their participation, participants were debriefed about the sham camera, and asked to complete a feedback questionnaire to assess acceptability of the research study. Participants were reimbursed for travel, and reimbursed with £10 for each research session. For non-clinical individuals who were unable to attend two separate sessions (e.g., due to long travel), sessions 1 and 2 were joined into one longer session. All assessments for the joined sessions were completed in the same order as in assessments on separate days.
6.2.3.5 Premature Withdrawal

If participants decided to withdraw prematurely they were free to do so, without the need to justify their decision. Any data collected until that point was retained unless requested otherwise by the participant. As with all other participants, they were offered a follow-up phone call to discuss any issues raised from the research.

Figure 6.1 – Flow diagram of study procedures
6.2.4 Ethical Considerations

6.2.4.1 Ethical Approval

The present study was assessed and approved by several committees. The Research Committee of the SLaM Psychosis CAG approved the study proposal on February 12th 2015 (CAG Reference: PSYR&D14/009; Appendix IX). The Risk Assessment Committee of King’s College London approved the study protocol as within an acceptable level of risk on March 24th 2015 (Appendix X). Full approval by the NHS Research Ethics Sub-Committee (NRES) London-Dulwich was granted on August 6th 2015 (REC Reference: 15/LO/0880; Appendices XI - XIV).

6.2.4.2 Assessment of Safety

No serious adverse events, i.e. situations that pose a serious threat to the physical and/or psychological wellbeing to participants and require medical or otherwise professional intervention, were expected to occur during this study. The dexamethasone suppression test has been found to have a very low side effect profile and is considered safe to use in psychiatric samples. Similarly, both the assessment of stressful life events and psychotic symptoms, as well as the exposure to psychosocial stress paradigms such as the Cold Pressor Test, have been extensively practiced in mental health research and participant groups such as the ones in the present study. A study doctor was available to consult/advice if appropriate during the eligibility screening, conduct an assessment and arrange any further care should any participant report adverse effects. Should a serious adverse event have occurred, this would have been immediately reported to both the REC and the sponsor, the protocol would have been adapted in order to minimise the risk of reoccurrence and feasibility of the study would have been reconsidered if necessary. Additionally, a Research Interview and Distress Protocol (Appendix XV) was put in place in line with existing guidelines (Draucker, Martsolf, and Poole, 2009), to ensure a systematic approach to managing any potential participant distress.
Preventive measures were taken to reduce the risk of adverse events and ensure optimal participant experience. Service user and participant representatives reviewed the methodology and judged it to be tolerable. Adverse events, such as distress in participants, would have been immediately reported and discussed within the research team, led to changes in our research procedures, and, if considered significant, the REC and sponsor would have been informed.

6.2.5 Statistical Analyses

6.2.5.1 Questionnaire Measures

All statistical analyses were carried out using SPSS for Windows (IBM Corp., 2015), and additionally JASP (JASP Team, 2016) was used for Bayesian analysis to express likelihood of data supporting the hypotheses. P-values below the 0.05 two-tailed threshold were accepted as statistically significant. In instances of multiple post-hoc testing, False Discovery Rate (FDR)-adjusted p-values are reported (Benjamini and Hochberg, 1995). Bayes factors of 3 and above were interpreted as sufficient evidence for the alternative hypothesis, and Bayes factors of 1/3 and below as sufficient evidence for the null hypothesis (Kass and Raftery, 1995). Bayesian statistics were carried out to provide an additional metric to evaluate findings with greater confidence. Additionally, effect sizes were calculated and converted to Cohen’s d to allow for comparison across effects. For three-way chi-square analyses, Cramer’s v is reported, which has similar effect size scaling to Cohen’s d. Effect size conversions were carried out using formulas commonly used in meta-analyses and research synthesis (Borenstein et al., 2009; Cooper et al., 2009; Fritz et al., 2012; Lipsey et al., 2001; Morris and DeShon, 2002). Normal distribution of data was checked by Q-Q plots and Kolmogorov-Smirnov tests, and Levene’s test was used to assess homogeneity of variance. Cronbach’s α was assessed for all questionnaire measure to ensure reliability.

For group comparisons of sociodemographic and questionnaire data, separate analyses were carried out for each questionnaire variable (dependent variables); with group (i.e., CVH vs HVH
vs HC) as the independent variable. Chi-square analyses were carried out for binary dependent variables. Normality of continuous variables was examined by visual inspection of Q-Q plots, as well as the Kolmogorov-Smirnov test. For 3-way comparisons, homogeneity of variance was additionally confirmed using Levene’s test. For normally distributed data, independent samples t-tests (CVH vs HVH) and ANOVA (CVH v HVH vs HC) were used for group comparisons on continuous variables. For post-hoc group comparisons, Tukey’s HSD was chosen. In group comparisons for non-normally distributed continuous variables, non-parametric Mann-Whitney U (CVH vs HVH) and Kruskall-Wallis (CVH vs HVH vs HC) tests were used. When total group comparisons showed significance, lower-order post-hoc comparisons were carried out.

For analysis of subjective stress levels during the SECPT, a repeated-measures mixed ANOVA was carried out on total VAS scores (DV) (within-participant independent variable) and group as the between-participants independent variable. For recovery of subjective stress-levels, paired-samples t-tests within groups were carried out on VAS scores from post-SECPT to 15min.

### 6.2.5.2 Saliva Data

For all cortisol and α-amylase analyses, associations of dependent variables with potential covariates, including BMI, age, gender and menstrual cycle/contraceptive pill, were assessed and included as covariates if significant. To establish normal distribution of cortisol and α-amylase data, logarithmic transformations (log$_e$) were undertaken for all analyses.

For assessment of baseline stress-function, repeated-measures ANCOVA using group as the independent variable and cortisol at 3pm and 8pm and α-amylase values at all three time points as the dependent variables was carried out. For assessment of morning cortisol, one-way ANCOVA was carried out. For cortisol, bivariate correlation analyses showed no significant covariates. For α-amylase, progesterone treatment was identified as a potential covariate. Further, outlier analyses were undertaken via assessment of interquartile ranges and extreme
values (i.e., those outside Q1 – 3 * IQR and Q3 + 3 * IQR) were excluded. This procedure was carried out due to the risk of faulty saliva sample self-administration or non-compliance with sampling instructions (e.g., participants may have had something to drink, thereby decreasing biomarker level concentrations artificially). Non-compliance rates in cortisol home sampling procedures may go as high as 30% (Broderick, Arnold, Kudielka, and Kirschbaum, 2004), and thus outlier exclusion at the cost of statistical power was decided upon as the most prudent approach.

To assess outcome of the dexamethasone suppression test, participants were classified as suppressors or non-suppressors, in line with the literature (Bradley and Dinan, 2010). As suggested by Cassidy et al. (2000), a cut-off value was assigned to all three sampling time points on the day following dexamethasone administration. In line with recent research on GR function (Castro, Elias, Quidute, Halah, and Moreira, 1999; Chriguer et al., 2005) as well as comparison of plasma and salivary cortisol response to dexamethasone (Ansseau et al., 1984), a cut-off cortisol value of 2.6nmol/L was decided upon. Thus, participants who had a cortisol value above 2.6nmol/L for any of their three samples were classified as non-suppressors. Likelihood chi-square analysis was carried out to investigate significant differences between groups, with lower-order post-hoc analyses for individual group differences.

For assessment of salivary cortisol and α-amylase response to the SECPT, repeated-measures ANCOVAs were carried out with group as the between-participants IV, time point as the within participants IV and log-transformed cortisol and α-amylase as the DV. For cortisol, bivariate correlations revealed current oral contraceptives (progesterone) as a potential covariate. For α-amylase, menstrual phase was identified as a potential covariate. Post-hoc testing of group-specific outcomes was carried out via pairwise comparisons as well as lower order ANOVAs for specific time points. For assessments of peak cortisol and α-amylase responses between groups, repeated-measures ANCOVAs for cortisol and α-amylase (with the covariates identified above)
were carried out from post-SECPT to 15min for cortisol, and pre-SECPT to post-SECPT for α-amylase.

### 6.3 Results

#### 6.3.1 Sample Characteristics

The present study recruited 23 CVHs, 27 HVHs, and 23 HCs. Three CVH participants withdrew after their first assessment and did not provide any saliva data, and two HVHs could not be assessed on saliva data due to significant physical illness deemed likely to skew results (one participant with a pituitary gland tumour, one participant on high dose steroid treatments). Their questionnaire data were therefore excluded from the present analyses. Thus, the final sample reported on here comprised 20 CVHs, 25 HVHs and 23 HCs.

Sample sizes per measure are shown in Table 6.5. Two CVHs and seven HVHs did not consent to taking the dexamethasone. Three HCs did not return their home saliva sampling packs. Two HVHs were not available to attend the SECPT session. For awakening cortisol, two outliers (i.e., values outside Q1 – 3 * IQR and Q3 + 3 * IQR; 1 CVH, 1 HC) were removed. For saliva samples on the baseline day, eleven samples did not contain sufficient amounts of saliva to be analysed for cortisol (1 CVH, 6 HVH, 4 HC), and one could not be analysed for α-amylase (1 CVH). For diurnal cortisol, two outliers were identified and removed (1 CVH, 1 HVH), and for diurnal a-amylase, two outliers were removed (1 CVH, 1 HVH).

No adverse events occurred during any of the study procedures. Participant groups did not differ significantly on age, ethnicity, and first language. However, group differences were found for gender, employment status, living status, relationship status, education level and body-mass index. Group specific differences are presented in Table 6.6. Clinical characteristics of CVHs are presented in Table 6.7.
### Table 6.5 – Sample sizes per measure

<table>
<thead>
<tr>
<th>Measure</th>
<th>CVHs</th>
<th>HVHs</th>
<th>HCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionnaires</td>
<td>20</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>Awakening Cortisol</td>
<td>19</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Diurnal Cortisol/ a-Amylase*</td>
<td>20</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>DST</td>
<td>18</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>SECPT</td>
<td>20</td>
<td>23</td>
<td>23</td>
</tr>
</tbody>
</table>

Note: * = N may differ on individual time points
Table 6.6 – Sample demographics (Mean ± SD, [% Exposed])

<table>
<thead>
<tr>
<th></th>
<th>CVHs (n = 20)</th>
<th>HVHs (n = 25)</th>
<th>HCs (n = 23)</th>
<th>Statistics</th>
<th>CVH vs HVH</th>
<th>CVH vs HC</th>
<th>HVH vs HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47.7 ± 8.5</td>
<td>45.24 ± 14.4</td>
<td>45.2 ± 10.4</td>
<td>F (67) = 0.3, p = 0.7, d = 0.2, BF10 = 0.1</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Gender (%) Female</td>
<td>35.0%</td>
<td>64.0%</td>
<td>30.4%</td>
<td>χ² = 6.5, p = 0.04, v = 0.31, BF10 = 2.4</td>
<td>χ² = 3.7, p = 0.05, d = 0.60, BF10 = 2.2</td>
<td>χ² = 0.1, p = 0.75, d = 0.10, BF10 = 0.4</td>
<td>χ² = 5.4, p = 0.02, d = 0.71, BF10 = 4.9</td>
</tr>
<tr>
<td>Ethnicity (% White British)</td>
<td>65.0%</td>
<td>52.0%</td>
<td>69.0%</td>
<td>χ² = 0.8, p = 0.7, v = 0.11, BF10 = 0.2</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>First Language (%) English</td>
<td>75.0%</td>
<td>80.0%</td>
<td>87.0%</td>
<td>χ² = 1.0, p = 0.6, v = 0.12, BF10 = 0.1</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Employment (%) Unemployed</td>
<td>100.0%</td>
<td>16%</td>
<td>8.7%</td>
<td>χ² = 46.0, p &lt; 0.001, v = 0.82, BF10 = 7.2 x 10⁹</td>
<td>χ² = 31.5, p &lt; 0.001, d = 3.06, BF10 = 2.5 x 10⁷</td>
<td>χ² = 35.7, p &lt; 0.001, d = 4.42, BF10 = 3.6 x 10⁸</td>
<td>χ² = 0.6, p = 0.4, d = 0.23, BF10 = 0.3</td>
</tr>
<tr>
<td>Living Status (%) Alone</td>
<td>57.1%</td>
<td>16.0%</td>
<td>17.4%</td>
<td>χ² = 12.8, p = 0.002, v = 0.43, BF10 = 30.6</td>
<td>χ² = 9.4, p = 0.002, d = 1.03, BF10 = 34.2</td>
<td>χ² = 8.3, p = 0.004, d = 0.89, BF10 = 22.0</td>
<td>χ² = 0.1, p = 0.9, d = 0.09, BF10 = 0.3</td>
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<td>Relationship Status (%) Single</td>
<td>60.0%</td>
<td>24.0%</td>
<td>43.5%</td>
<td>χ² = 6.0, p = 0.049, v = 0.30, BF10 = 2.1</td>
<td>χ² = 6.0, p = 0.01, d = 1.03, BF10 = 6.5</td>
<td>χ² = 1.2, p = 0.28, d = 0.34, BF10 = 0.6</td>
<td>χ² = 2.0, p = 0.2, d = 0.42, BF10 = 0.9</td>
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<td>Education Level No Qualifications:</td>
<td>25.0%</td>
<td>0.0%</td>
<td>4.3%</td>
<td>χ² = 19.4, p = 0.01, v = 0.38, BF10 = 13.8</td>
<td>χ² = 12.3, p = 0.02, d = 1.23, BF10 = 23.4</td>
<td>χ² = 12.3, p = 0.02, d = 1.27, BF10 = 20.8</td>
<td>χ² = 5.8, p = 0.2, d = 0.74, BF10 = 0.2</td>
</tr>
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<td>GCSE/O' Levels:</td>
<td>20.0%</td>
<td>16.0%</td>
<td>0.0%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>A’ Levels:</td>
<td>10.0%</td>
<td>8.0%</td>
<td>13.0%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Vocational/College:</td>
<td>25.0%</td>
<td>12.0%</td>
<td>21.7%</td>
<td>-</td>
<td>-</td>
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<td></td>
</tr>
<tr>
<td>University/Professional:</td>
<td>20.0%</td>
<td>64.0%</td>
<td>60.9%</td>
<td>-</td>
<td>-</td>
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<td></td>
</tr>
<tr>
<td>Body-Mass Index</td>
<td>31.1 ± 7.6</td>
<td>26.9 ± 6.7</td>
<td>24.5 ± 4.4</td>
<td>F (62) = 5.7, p = 0.006, d = 0.84, BF10 = 4.9</td>
<td>Tukey HSD p = 0.10</td>
<td>Tukey HSD p = 0.004</td>
<td>Tukey HSD p = 0.40</td>
</tr>
<tr>
<td>Water Temperature (°C)</td>
<td>0.4 ± 0.5</td>
<td>0.5 ± 0.7</td>
<td>0.3 ± 0.3</td>
<td>F (63) = 0.8, p = 0.46, d = 0.31, BF10 = 0.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SECPT Time in water (mm:ss)</td>
<td>02:18 ± 00:57</td>
<td>02:26 ± 01:01</td>
<td>02:41 ± 00:36</td>
<td>F (63) = 1.1, p = 0.35, d = 0.37*</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Day 1 Awakening (hh:mm)</td>
<td>7:56 ± 1:22</td>
<td>7:15 ± 1:31</td>
<td>7:05 ± 1:15</td>
<td>F (48) = 1.5, p = 0.23, d = 0.51*</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Day 2 Awakening (hh:mm)</td>
<td>7:52 ± 1:40</td>
<td>7:46 ± 1:39</td>
<td>7:31 ± 1:02</td>
<td>F (55) = 0.3, p = 0.77, d = 0.20*</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Note: Bold + italics = significant p-value; d = Cohen’s d; v = Cramer’s v; BF = Bayes Factor; * = Bayesian ANOVA for time data not possible in JASP
Table 6.7 – Clinical characteristics CVHs (n, %)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia:</td>
<td>11, 55%</td>
</tr>
<tr>
<td>Schizoaffective Disorder:</td>
<td>1, 5%</td>
</tr>
<tr>
<td>Psychosis NOS:</td>
<td>3, 15%</td>
</tr>
<tr>
<td>Other Affective Disorders:</td>
<td>5, 25%</td>
</tr>
</tbody>
</table>

Psychiatric Medications

- Typical Antipsychotics: 0, 0%
- Atypical Antipsychotics: 11, 55%
- Clozapine: 6, 30%
- No Antipsychotics: 3, 15%
- Antidepressants: 9, 45%
- Mood Stabilisers: 3, 15%

6.3.2 Questionnaire Results

Sensitivity analyses using G*Power for Windows (Faul et al., 2007) indicated that the present analyses were powered to detect group difference effect sizes of Cohen’s d = 0.77, at β = 0.8.

Assessment of substance use between groups using Kruskal-Wallis H tests revealed no significant differences in lifetime use, age of first use, current use or frequency of use for alcohol, tobacco, cannabis or amphetamines. Results are present in Table 6.8.
### Table 6.8 – Substance use between groups (Means ± SD unless specified otherwise)

<table>
<thead>
<tr>
<th>Substance</th>
<th>CVHs (n = 20)</th>
<th>HVHs (n = 25)</th>
<th>HCs (n = 23)</th>
<th>Group Statistics (chi-squares for frequency data; Kruskal-Wallis for continuous data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime Use:</td>
<td>95.0%</td>
<td>96.0%</td>
<td>100.0%</td>
<td>( \chi^2 = 1.1, p = 0.58, v = 0.13, BF_{10} = 0.2 ) ( \chi^2 = 0.51, p = 0.79, d = 0.29, BF_{10} = 0.2 ) ( \chi^2 = 2.8, p = 0.25, v = 0.21, BF_{10} = 0.5 )</td>
</tr>
<tr>
<td>Age of Onset:</td>
<td>13.1 ± 4.1</td>
<td>13.7 ± 4.4</td>
<td>14.6 ±3.5</td>
<td></td>
</tr>
<tr>
<td>Current Use:</td>
<td>78.9%</td>
<td>66.7%</td>
<td>87.0%</td>
<td></td>
</tr>
<tr>
<td>Frequency*:</td>
<td>3.6 ± 1.3</td>
<td>3.3 ± 1.4</td>
<td>2.8 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>Tobacco</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime Use:</td>
<td>85.0%</td>
<td>68.0%</td>
<td>82.6%</td>
<td></td>
</tr>
<tr>
<td>Age of Onset:</td>
<td>18.2 ± 9.4</td>
<td>17.2 ± 3.6</td>
<td>16.2 ± 3.8</td>
<td></td>
</tr>
<tr>
<td>Current Use:</td>
<td>52.9%</td>
<td>23.5%</td>
<td>26.4%</td>
<td></td>
</tr>
<tr>
<td>Frequency*:</td>
<td>3.7 ± 1.8</td>
<td>3.3 ± 1.9</td>
<td>3.2 ± 2.0</td>
<td></td>
</tr>
<tr>
<td>Cannabis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime Use:</td>
<td>80.0%</td>
<td>60.0%</td>
<td>78.3%</td>
<td></td>
</tr>
<tr>
<td>Age of Onset:</td>
<td>19.1 ± 5.1</td>
<td>18.7 ± 3.7</td>
<td>20.7 ± 6.6</td>
<td></td>
</tr>
<tr>
<td>Current Use:</td>
<td>6.3%</td>
<td>6.7%</td>
<td>11.1%</td>
<td></td>
</tr>
<tr>
<td>Frequency*:</td>
<td>3.0 ± 1.9</td>
<td>2.8 ± 1.7</td>
<td>2.6 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>Amphetamines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime Use:</td>
<td>45.0%</td>
<td>36.0%</td>
<td>47.8%</td>
<td></td>
</tr>
<tr>
<td>Age of Onset:</td>
<td>22.8 ± 4.7</td>
<td>22.6 ± 9.0</td>
<td>21.1 ± 3.6</td>
<td></td>
</tr>
<tr>
<td>Current Use:</td>
<td>22.2%</td>
<td>11.1%</td>
<td>9.1%</td>
<td></td>
</tr>
<tr>
<td>Frequency*:</td>
<td>2.7 ± 1.3</td>
<td>2.7 ± 1.2</td>
<td>3.8 ± 4.5</td>
<td></td>
</tr>
</tbody>
</table>

Note: * = if not currently using, the highest previous frequency of use; d = Cohen's d; BF = Bayes Factor.
Kruskal-Wallis H analyses showed significant differences for total DASS scores across groups, as well as for Depression, Anxiety and Stress subscales. Specifically, CVHs showed higher levels on total DASS scores as well as all subscales compared to both HVHs and HCs, who did not differ from each other. Kruskal-Wallis H analysis also showed significantly lower FFMQ scores in CVHs compared to both HVHs and HCs, who again did not differ from each other (see Table 6.9).

Kruskal-Wallis H analyses further identified significant group differences for total endorsed CAPS scores. Specifically, CVHs and HVHs endorsed significantly more items than HCs, but did not differ from each other. Similarly, the Intrusiveness subscale scores showed significantly lower scores for HCs, with no differences between CVHs and HVHs. For Distress and Frequency subscales, CVHs had significantly higher scores than HVHs and HCs, and HVHs had significantly higher scores than HCs. Groups differed significantly on total and physical abuse scores of the SLESQ, but not sexual abuse scores. Paired comparisons showed that CVHs had significantly higher scores on total scores compared to HCs, whilst HVHs differed from neither CVHs nor HCs. For physical abuse, CVHs had significantly higher scores than both HCs and HVHs, who did not significantly differ from each other. Questionnaire results are presented in Table 6.9.
Table 6.9 – Questionnaire results (Mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>CVHs (n = 20)</th>
<th>HVHs (n = 25)</th>
<th>HCs (n = 23)</th>
<th>Group Statistics</th>
<th>CVH vs HVH</th>
<th>CVH vs HC</th>
<th>HVH vs HC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAPS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>15.9 ± 6.8</td>
<td>13.4 ± 6.7</td>
<td>2.0 ± 2.8</td>
<td>$\chi^2 = 39.9$, $p &lt; 0.001$, $d = 2.38$, BF$_{10} = 5.8 \times 10^8$</td>
<td>U = 202, Z = 1.1, p = 0.27, d = 0.21, BF$_{10} = 0.5$</td>
<td>U = 8, Z = 5.5, p &lt; 0.001, d = 2.91, BF$_{10} = 2.3 \times 10^6$</td>
<td>U = 29, Z = 5.4, p &lt; 0.001, d = 2.41, BF$_{10} = 7.1 \times 10^6$</td>
</tr>
<tr>
<td><strong>Intrusiveness</strong></td>
<td>3.1 ± 0.8</td>
<td>2.6 ± 0.9</td>
<td>1.3 ± 0.5</td>
<td>$\chi^2 = 38.4$, $p &lt; 0.001$, $d = 2.28$, BF$_{10} = 3.8 \times 10^7$</td>
<td>U = 180, Z = 1.6, p = 0.11, d = 0.38, BF$_{10} = 0.7$</td>
<td>U = 14, Z = 5.4, p &lt; 0.001, d = 2.70, BF$_{10} = 5.4 \times 10^7$</td>
<td>U = 37, Z = 5.2, p &lt; 0.001, d = 2.24, BF$_{10} = 92968.7$</td>
</tr>
<tr>
<td><strong>Distress</strong></td>
<td>3.1 ± 1.0</td>
<td>1.6 ± 0.6</td>
<td>1.3 ± 0.6</td>
<td>$\chi^2 = 36.5$, $p &lt; 0.001$, $d = 2.15$, BF$_{10} = 4.8 \times 10^6$</td>
<td>U = 41, Z = 4.8, p &lt; 0.001, d = 1.97, BF$_{10} = 91880.2$</td>
<td>U = 20, Z = 5.3, p &lt; 0.001, d = 2.52, BF$_{10} = 1.9 \times 10^6$</td>
<td>U = 180, Z = 2.4, p = 0.02, d = 0.68, BF$_{10} = 0.8$</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>3.4 ± 0.8</td>
<td>1.7 ± 0.7</td>
<td>1.3 ± 0.6</td>
<td>$\chi^2 = 40.2$, $p &lt; 0.001$, $d = 2.41$, BF$_{10} = 3.1 \times 10^{11}$</td>
<td>U = 24, Z = 1.6, p &lt; 0.001, d = 2.38, BF$_{10} = 5.2 \times 10^6$</td>
<td>U = 11, Z = 5.4, p &lt; 0.001, d = 2.80, BF$_{10} = 1.0 \times 10^9$</td>
<td>U = 167, Z = 2.6, p = 0.01, d = 0.77, BF$_{10} = 1.3$</td>
</tr>
<tr>
<td><strong>DASS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>53.0 ± 27.3</td>
<td>14.6 ± 16.1</td>
<td>11.8 ± 10.8</td>
<td>$\chi^2 = 29.9$, $p &lt; 0.001$, $d = 1.77$, BF$_{10} = 3.2 \times 10^7$</td>
<td>U = 47, Z = 4.6, p &lt; 0.001, d = 1.85, BF$_{10} = 21408.7$</td>
<td>U = 29, Z = 4.9, p &lt; 0.001, d = 2.29, BF$_{10} = 202346.0$</td>
<td>U = 258, Z = 0.4, p = 0.66, d = 0.18, BF$_{10} = 0.4$</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>20.4 ± 12.6</td>
<td>3.1 ± 4.9</td>
<td>3.5 ± 4.2</td>
<td>$\chi^2 = 28.7$, $p &lt; 0.001$, $d = 1.71$, BF$_{10} = 7.8 \times 10^7$</td>
<td>U = 45, Z = 4.7, p &lt; 0.001, d = 1.89, BF$_{10} = 76829.3$</td>
<td>U = 43, Z = 4.6, p &lt; 0.001, d = 1.99, BF$_{10} = 311634.4$</td>
<td>U = 258, Z = 0.6, p = 0.53, d = 0.18, BF$_{10} = 0.3$</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td>14.7 ± 8.3</td>
<td>3.2 ± 4.7</td>
<td>1.9 ± 2.4</td>
<td>$\chi^2 = 34.7$, $p &lt; 0.001$, $d = 2.04$, BF$_{10} = 1.2 \times 10^8$</td>
<td>U = 39, Z = 4.9, p &lt; 0.001, d = 2.01, BF$_{10} = 18834.4$</td>
<td>U = 12, Z = 5.4, p &lt; 0.001, d = 2.77, BF$_{10} = 661078.0$</td>
<td>U = 260, Z = 0.6, p = 0.56, d = 0.16, BF$_{10} = 0.5$</td>
</tr>
<tr>
<td><strong>Stress</strong></td>
<td>18.0 ± 10.3</td>
<td>8.3 ± 7.3</td>
<td>6.3 ± 6.1</td>
<td>$\chi^2 = 17.2$, $p &lt; 0.001$, $d = 1.04$, BF$_{10} = 1014.8$</td>
<td>U = 104, Z = 3.4, p &lt; 0.001, d = 1.06, BF$_{10} = 45.7$</td>
<td>U = 77, Z = 3.8, p &lt; 0.001, d = 1.46, BF$_{10} = 436.2$</td>
<td>U = 237, Z = 1.1, p = 0.29, d = 0.30, BF$_{10} = 0.4$</td>
</tr>
<tr>
<td><strong>FFMQ</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>107.3 ± 17.2</td>
<td>139.3 ± 14.1</td>
<td>135 ± 19.3</td>
<td>$\chi^2 = 26.9$, $p &lt; 0.001$, $d = 1.16$, BF$_{10} = 299171.1$</td>
<td>U = 34, Z = 4.9, p &lt; 0.001, d = 2.12, BF$_{10} = 430225.2$</td>
<td>U = 66, Z = 4.0, p &lt; 0.001, d = 1.61, BF$_{10} = 1246.7$</td>
<td>U = 254, Z = 0.7, p = 0.48, d = 0.20, BF$_{10} = 0.4$</td>
</tr>
<tr>
<td></td>
<td>CVHs (n = 20)</td>
<td>HVHs (n = 25)</td>
<td>HCs (n = 23)</td>
<td>Group Statistics</td>
<td>CVH vs HVH</td>
<td>CVH vs HC</td>
<td>HVH vs HC</td>
</tr>
<tr>
<td>--------</td>
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<td>----------</td>
</tr>
<tr>
<td>Sexual</td>
<td>5.6 ± 2.2, 100%</td>
<td>4.7 ± 2.7, 92.0%</td>
<td>3.2 ± 2.9, 95.7%</td>
<td>$\chi^2 = 9.0, p = 0.01, d = 0.78, BF_{10} = 3.1$</td>
<td>$U = 209, Z = 1.0, p = 0.34, d = 0.16, BF_{10} = 0.5$</td>
<td>$U = 102, Z = 3.1, p = 0.002, d = 1.17, BF_{10} = 10.3$</td>
<td>$U = 203, Z = 1.8, p = 0.076, d = 0.52, BF_{10} = 1.0$</td>
</tr>
<tr>
<td>Physical</td>
<td>4.3 ± 2.2, 85.0%</td>
<td>2.2 ± 2.2, 64.0%</td>
<td>1.9 ± 2.6, 43.5%</td>
<td>$\chi^2 = 10.7, p = 0.01, d = 0.86, BF_{10} = 8.4$</td>
<td>$U = 138, Z = 2.6, p = 0.01, d = 0.73, BF_{10} = 6.5$</td>
<td>$U = 114, Z = 2.9, p = 0.004, d = 1.05, BF_{10} = 9.0$</td>
<td>$U = 242, Z = 1.0, p = 0.32, d = 0.27, BF_{10} = 0.3$</td>
</tr>
</tbody>
</table>

Note: CAPS = Cardiff Anomalous Perceptions Scale; DASS = Depression Anxiety Stress Scale; FFMQ = Five Facet Mindfulness Questionnaire; SLESQ = Stressful Life Events Screening Questionnaire; bold + italics = significant p-value; $\chi^2$ = Kruskal-Wallis H test; d = Cohen’s d; BF = Bayes Factor
Comparing AVH parameters between CVHs and HVHs, CVHs had significantly higher scores on Frequency, Loudness and Distress subscales of the PSYRATS, but did not differ on the attribution subscale. HVHs had a significantly earlier age of onset of AVHs. On the BAVQ-R, CVHs scored significantly higher on the Malevolence, Omnipotence and Resistance subscales, and significantly lower on the Benevolence and Engagement subscales. On the VPDS, total scores (excluding the Harm item) did not differ significantly between the groups. Scores on the Harm item (for those participants who endorsed it) were significantly higher for CVHs. AVH-specific questionnaire results are showed in Table 6.10.

Table 6.10 – AVH results (Mean ± SD unless specified otherwise)

<table>
<thead>
<tr>
<th></th>
<th>CVHs (n = 20)</th>
<th>HVHs (n = 25)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSYRATS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>7.0 ± 2.0</td>
<td>3.3 ± 1.1</td>
<td>U = 15, Z = 5.5, p &lt; 0.001, d = 2.67, BF&lt;sub&gt;10&lt;/sub&gt; = 4.0 x 10&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Loudness</td>
<td>2.1 ± 0.9</td>
<td>1.4 ± 0.8</td>
<td>U = 138, Z = 2.8, p = 0.005, d = 0.83, BF&lt;sub&gt;10&lt;/sub&gt; = 4.4</td>
</tr>
<tr>
<td>Attribution</td>
<td>5.3 ± 1.4</td>
<td>5.7 ± 1.1</td>
<td>U = 407, Z = 1.4, p = 0.20, d = 1.27, BF&lt;sub&gt;10&lt;/sub&gt; = 0.5</td>
</tr>
<tr>
<td>Distress</td>
<td>16.2 ± 3.8</td>
<td>1.5 ± 2.0</td>
<td>U = 1, Z = 5.7, p &lt; 0.001, d = 3.20, BF&lt;sub&gt;10&lt;/sub&gt; = 7.3 x 10&lt;sup&gt;16&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age of Onset</td>
<td>27.3 ± 11.4</td>
<td>15.3 ± 11.2</td>
<td>t (43) = 3.5, p = 0.001, BF&lt;sub&gt;10&lt;/sub&gt; = 30.4</td>
</tr>
<tr>
<td>BAVQ-R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malevolence</td>
<td>16.9 ± 5.3</td>
<td>6.2 ± 0.8</td>
<td>U = 2, Z = 6.1, p &lt; 0.001, d = 3.15, BF&lt;sub&gt;10&lt;/sub&gt; = 4.7 x 10&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Benevolence</td>
<td>9.3 ± 3.7</td>
<td>19.7 ± 4.9</td>
<td>U = 31, Z = 5.0, p &lt; 0.001, d = 2.24, BF&lt;sub&gt;10&lt;/sub&gt; = 1.0 x 10&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Omnipotence</td>
<td>17.2 ± 4.4</td>
<td>12.0 ± 3.1</td>
<td>t (33) = 4.4, p &lt; 0.001, d = 1.32, BF&lt;sub&gt;10&lt;/sub&gt; = 494.9</td>
</tr>
<tr>
<td>Resistance</td>
<td>28.1 ± 5.7</td>
<td>10.4 ± 2.5</td>
<td>t (25) = 13.9, p &lt; 0.001, d = 4.17, BF&lt;sub&gt;10&lt;/sub&gt; = 1.9 x 10&lt;sup&gt;14&lt;/sup&gt;</td>
</tr>
<tr>
<td>Engagement</td>
<td>10.0 ± 2.4</td>
<td>25.8 ± 6.0</td>
<td>U = 16.5, Z = 5.4, p &lt; 0.001, d = 2.62, BF&lt;sub&gt;10&lt;/sub&gt; = 1.6 x 10&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>VPDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>20.2 ± 5.9</td>
<td>19.2 ± 3.5</td>
<td>U = 212, Z = 0.9, p = 0.38, d = 0.26, BF&lt;sub&gt;10&lt;/sub&gt; = 0.4</td>
</tr>
<tr>
<td>Harm Item (%) answered</td>
<td>100%, 4.1 ± 1.1</td>
<td>44.0%, 2.7 ± 1.1</td>
<td>U = 48, Z = -2.7, p = 0.008, d = 1.90, BF&lt;sub&gt;10&lt;/sub&gt; = 9.9</td>
</tr>
</tbody>
</table>

Note: bold + italics = significant p-value; d = Cohen’s d; BF = Bayes Factor
6.3.3 Baseline Stress Function

*Hypothesis: CVHs will show significantly higher morning cortisol levels compared to HVHs and HCs, who will not differ from each other.*

Sensitivity analyses using G*Power for Windows (Faul et al., 2007) indicated that the present analyses were powered to detect group difference effect sizes of Cohen’s $d = 0.82$, at $\beta = 0.8$. One-way ANOVA showed that there were no significant differences in awakening time on Day 1 ($F (2, 48) = 1.5, p = 0.23, d = 0.51$), or Day 2 ($F (2, 55) = 0.3, p = 0.77, d = 0.20$), confirming equal awakening times across groups (see Table 6.6). However, only 49 out of 64 participants provided these data for Day 1, and 56 did so for Day 2.

One-way ANOVA showed a significant effect of group on morning cortisol levels ($F (2, 55) = 4.5, p = 0.015, d = 0.81, BF_{10} = 3.6$). Contrary to predictions, pairwise comparisons with FDR-adjusted p-values showed that cortisol levels were significantly lower (rather than higher) for CVHs ($M_{\text{logn}} = 1.5, SD = 0.2$) than for HVHs ($M_{\text{logn}} = 2.4, SD = 0.2; p = 0.02, d = 4.5, BF_{10} = 4.3$), and HCs ($M_{\text{logn}} = 2.1, SD = 0.2; p = 0.03, d = 3.0, BF_{10} = 1.7$), who did not differ from each other ($p = 0.66, d = 1.5, BF_{10} = 0.4$). Cortisol awakening results are presented in Figure 6.2.
Figure 6.2 – Log$_n$ cortisol levels at awakening by group (mean ± SE)

Hypothesis: CVHs will show significantly higher diurnal cortisol and α-amylase levels compared to HVHs and HCs, who will not differ from each other.

Sensitivity analyses using G*Power for Windows (Faul et al., 2007) indicated that the present analyses were powered to detect effect sizes of Cohen’s $d =$ 0.38 for cortisol and $d =$ 0.36 for α-amylase, at $\beta =$ 0.8.

Repeated-measures ANOVA showed a significant effect of time on cortisol ($F (1, 53) =$ 19.3, $p < 0.001$, $d =$ 0.53, $BF_{10} =$ 231.8), with overall higher scores at the 3pm timepoint compared to the 8pm timepoint. Contrary to predictions, there was no significant group effect ($F (2, 53) =$ 0.01, $p =$ 0.99, $d =$ 0.00, $BF_{10} =$ 0.17), and no interaction effect with group ($F (2, 53) =$ 2.5, $p =$ 0.09, $d =$ 0.17, $BF_{M} =$ 0.5).
For α-amylase levels over all three time-points, repeated-measures ANCOVA controlling for progesterone treatment found a significant effect of timepoint \((F (1.5, 85.8) = 4.0, p = 0.03, d = 0.42, BF_{10} = 5.1 \times 10^{14})\), with a general increase over the day (see Figure 6.3). Contrary to predictions, there was no significant group effect \((F (2, 55) = 0.78, p = 0.46, d = 0.34, BF_{10} = 0.28)\), and no interaction effect with group was observed \((F (1.5, 85.8) = 1.1, p = 0.34, d = 0.08, BF_{M} = 0.4)\).

**Figure 6.3** – Diurnal α-amylase levels (mean ± SE) by group

### 6.3.4 Dexamethasone Suppression Test

*Hypothesis: CVHs will show significantly less cortisol suppression following dexamethasone administration compared to HVHs and HCs, who will not differ from each other.*
Sensitivity analyses using G*Power for Windows (Faul et al., 2007) indicated that the present analyses were powered to detect group difference effect sizes of Cramer’s $v = 0.41$, at $\beta = 0.8$.

Classification of participants into suppressors or non-suppressors showed that a total of 33.9% of participants did not respond to the dexamethasone. Specifically, 55.6% of CVHs ($n = 10$), 33.3% of HVHs ($n = 6$), and 15% of HCs ($n = 3$), were non-suppressors. Likelihood ratio chi-square analysis showed this difference to be statistically significant ($\chi^2 = 7.2$, $p = .03$, $v = 0.35$, $BF_{10} = 3.5$). As predicted, post-hoc analyses using FDR-adjusted $p$-values revealed that CVHs were significantly more likely to be non-suppressors than HCs ($\chi^2 = 7.2$, $p = .03$, $d = 0.97$, $BF_{10} = 10.6$), whilst HVHs differed from neither CVHs ($\chi^2 = 1.8$, $p = .18$, $d = 0.45$, $BF_{10} = 0.9$) nor HCs ($\chi^2 = 1.8$, $p = .18$, $d = 0.45$, $BF_{10} = 0.75$). Results are presented in Figure 6.3.

![Figure 6.3 - Percentages of DST non-suppressors by group](image)

* = CVHs significantly differ from HCs

**Figure 6.4** – Percentages of DST non-suppressors by group
6.3.5 Socially Evaluative Cold Pressor Test

Sensitivity analyses using G*Power for Windows (Faul et al., 2007) indicated that the present analyses were powered to within-between interactions at effect sizes of Cohen’s $d = 0.28$, at $\beta = 0.8$. One-way ANOVA showed that there were no significant differences in water temperature between groups ($F (2, 63) = 0.8, p = 0.46, d = 0.31, BF_{10} = 0.2$), nor did participant groups differ in how long they kept their hand in the ice water ($F (2, 63) = 1.1, p = 0.35, d = 0.37$), confirming equal exposure across groups (see Table 6.6).

6.3.5.1 Subjective Response

Hypothesis: CVHs will show increased anticipatory stress appraisal before exposure and have higher subjective stress levels throughout the paradigm, including greater overall levels and diminished recovery (measured from Post-SECPT to 15min) compared to HVHs and HCs, who will not differ from each other.

One-way ANOVA showed significant group differences in anticipatory SAM scores prior to the task across groups ($F (2, 63) = 7.6, p = 0.001, d = 0.39, BF_{10} = 29.4$). As predicted, post-hoc comparison with FDR-adjusted $p$-values showed that this was due to significantly higher SAM scores in CVHs ($M = 23.2, SD = 1.6$) compared to both HVHs ($M = 17.1, SD = 1.5, p = 0.009$) and HCs ($M = 15.1, SD = 1.5, p = 0.003$), who did not differ from each other ($p = 0.35$).

Repeated measures ANOVA suggested a violation of Mauchly’s test of sphericity for VAS scores, and therefore the Greenhouse-Geisser statistic was used. This revealed a significant effect of timepoint on VAS scores ($F (1.9, 118.1) = 4.8, p = 0.01, d = 0.14, BF_{10} = 292.4$), but no significant interaction with group ($F (3.8, 118.1) = 0.62, p = 0.64, d = 0.04, BF_{M} = 0.03$). However, there was a significant effect of group on VAS scores ($F (2, 63) = 31.7, p < 0.001, d = 1.00, BF_{10} = 3.2 \times 10^3$), with post-hoc group comparison with FDR-adjusted $p$-values showing significantly higher VAS
scores in CVHs compared to both HVHs ($p = 0.002$) and HCs ($p = 0.002$), but no differences between HVHs and HCs ($p = 0.66$), as predicted.

In terms of recovery post-SECPT, HVHs ($t (24) = 2.5, p = 0.03, d = 0.59, BF_{10} = 2.3$) and HCs ($t (22) = 3.0, p = 0.02, d = 0.46, BF_{10} = 7.1$) showed a significant decrease in VAS scores from Post-SECPT to 15min, which was not observed in CVHs ($t (19) = 0.2, p = 0.86, d = 0.06, BF_{10} = 0.2$). FDR-adjusted $p$-values are reported. Subjective stress results are presented in Figure 6.5.

**Figure 6.5** – VAS scores by group by timepoint (mean ± SE)
6.3.5.2 Cortisol Response

Hypothesis: CVHs will show overall higher cortisol levels, coupled with a blunted cortisol response (indicated by blunted increase from post-SECPT to 15min) to the SECPT compared to HVHs and HCs, who will not differ from each other.

Repeated measures ANCOVA, controlling for oral contraceptives (progesterone), also suggested a violation of Mauchly’s test of sphericity for cortisol, and therefore the Greenhouse-Geisser statistic was used. This revealed a significant effect of timepoint on cortisol levels ($F(3.1, 191.8) = 15.9, p < 0.001, \text{d } = 0.41, \text{BF}_{10} = 4.0 \times 10^{12}$), as well as a significant interaction with group ($F(6.3, 191.8) = 2.8, p = 0.01, \text{d } = 0.17, \text{BF}_{M} = 8.4$). Test of between-participants effects showed trend-level significance ($F(2, 61) = 2.88, p = 0.064, \text{d } = 0.61, \text{BF}_{10} = 1.6$). Pairwise comparison showed that, as predicted, CVHs had trend-level higher cortisol levels than HVHs ($p = 0.07$), however, contrary to predictions they did not differ from HCs ($p = 0.97$). Unexpectedly, HVHs also showed trend-level lower cortisol levels than HCs ($p = 0.07$). Lower order ANOVAs with FDR-adjusted post-hoc comparison revealed significant group differences at Baseline ($F(2, 63) = 5.0, p = 0.02, \text{d } = 0.28, \text{BF}_{10} = 5.2$; CVH vs HVH: $p = 0.01$, CVHs vs HC: $p = 0.50$, HVH vs HC: $p = 0.04$); Pre-SECPT ($F(2, 63) = 5.1, p = 0.02, \text{d } = 0.28, \text{BF}_{10} = 5.3$; CVH vs HVH: $p = 0.01$, CVHs vs HC: $p = 0.50$, HVH vs HC: $p = 0.04$), and 0min Post-SECPT ($F(2, 63) = 5.1, p = 0.02, \text{d } = 0.28, \text{BF}_{10} = 5.5$; CVH vs HVH: $p = 0.01$, CVHs vs HC: $p = 0.51$, HVH vs HC: $p = 0.04$), with lower cortisol in HVHs compared to both CVHs and HCs, who did not differ from each other.

To assess blunting of the peak cortisol response, repeated measures ANCOVA controlling for progesterone revealed a significant effect for time point on cortisol levels ($F(1, 62) = 19.0, p < 0.001, \text{d } = 1.11, \text{BF}_{10} = 343.1$), with a trend-effect effect of group on cortisol ($F(2, 62) = 2.7, p = 0.08, \text{d } = 0.59, \text{BF}_{10} = 1.4$), and a significant interaction effect of group and time point on cortisol ($F(2, 62) = 4.2, p = 0.02, \text{d } = 0.74, \text{BF}_{M} = 5.2$). Post-hoc paired-samples t-test within groups with FDR-adjusted p-values were carried out from pre-SECPT to 15min post-SECPT (i.e., peak cortisol
response), revealing that, as predicted, there was no significant change in cortisol levels in CVHs (t (19) = 0.5, p = 0.61, d = 0.03, BF_{10} = 0.2), whilst cortisol levels increased significantly in HVHs (t (22) = 3.0, p = 0.009, d = 0.48, BF_{10} = 9.0) and HCs (t(22) = 3.6, p = 0.006, d = 0.63, BF_{10} = 29.5).

Although no specific hypotheses were made regarding recovery rates, visual inspection further suggested differential recovery rates between time points 15min and 45min between HVHs and HCs. Paired-samples t-test within groups were carried out from 15min and 30min, and 30min and 45min post-SECPT within HVHs and HCs. HVHs showed no significant change in cortisol levels at 15min-30min (t (22) = 0.9, p = 0.37, d = 0.07, BF_{10} = 0.3), whilst their cortisol levels decreased significantly at 30min-45min (t (22) = 3.4, p = 0.008, d = 0.33, BF_{10} = 19.5). HCs showed a significant decrease in cortisol levels at 15min-30min (t (22) = 2.6, p = 0.04, d = 0.46, BF_{10} = 3.4), whilst cortisol levels did not change at 30min-45min (t (22) = 1.3, p = 0.29, d = 0.16, BF_{10} = 0.4). FDR-adjusted p-values are reported. Cortisol levels during the SECPT are presented in Figure 6.6.
Figure 6.6 – Logn cortisol values by group by timepoint (mean ± SE)

**6.3.5.3 α-Amylase Response**

_Hypothesis: CVHs will show an exacerbated α-amylase response to the SECPT (from pre-SECPT to post-SECPT) compared to HVHs and HCs, who will not differ from each other._

Repeated measures ANCOVA, controlling for menstrual cycle, also suggested a violation of Mauchly’s test of sphericity for α-amylase, and therefore the Greenhouse-Geisser statistic was used. This revealed no significant effects for timepoint on α-amylase levels (F (4.0, 244.4) = 0.7, p = 0.60, d = 0.24, BF10 = 0.02), nor was there an interaction with group (F (8.0, 244.4) = 0.8, p = 0.63, d = 0.19, BF10 = 4.0 x 10^{-4}). Test of between-participants effects showed no significant effect of group on α-amylase level (F (2, 61) = 0.1, p = 0.87, d = 0.01, BF10 = 0.4). Similarly, repeated measures ANCOVA investigating the peak α-amylase response revealed no significant
effect for time point on $\alpha$-amylose levels ($F(1, 61) = 1.2$, $p = 0.27$, $d = 1.00$, $BF_{10} = 0.5$), no effect of group on $\alpha$-amylose ($F(2, 61) = 0.2$, $p = 0.79$, $d = 0.18$, $BF_{10} = 0.6$), and no interaction effect of group and time point on $\alpha$-amylose ($F(2, 61) = 0.97$, $p = 0.38$, $d = 0.36$, $BF_{M} = 0.1$). $\alpha$-Amylose levels during the SECPT are presented in Figure 6.7.

Figure 6.7 – $\log_{10}$ $\alpha$-amylose values by group by timepoint (mean ± SE)

6.4 Discussion

6.4.1 Findings

The present study is, to our knowledge, the first to report several alterations of psychophysiological stress-functions specific to AVHs and need for care. The overall hypotheses were partially supported: there were significant differences on some, but not all, parameters between CVHs, and HVHs and HCs, although the differences found were not always in the predicted direction. Whilst HVHs and HCs were similar on most parameters, a few unexpected
results emerged, including increased rates of dexamethasone non-response in HVHs, and lower cortisol levels during the SECPT.

Contrary to the hypothesis, CVHs showed lower, rather than higher, awakening cortisol levels than both HVHs and HCs, who did not differ from each other. This finding contradicts the meta-analysis finding of exacerbated awakening cortisol levels in schizophrenia (Girshkin et al., 2014). However, that meta-analysis also found lower effect sizes in medicated compared to unmedicated patients, and in outpatients compared to inpatients; in addition, several other studies have reported a blunted cortisol awakening response in psychosis patients (Braehler et al., 2005; Mondelli et al., 2010, 2015; Monteleone et al., 2014; Pruessner, Cullen, Aasand Walker, 2017). Similarly, contrary to our hypotheses, no significant group differences for diurnal cortisol and α-amylase were found. The increased diurnal cortisol levels reported in schizophrenia (Pruessner et al., 2017), as well as increased α-amylase levels reported in other studies (Ieda et al., 2014; Inagaki et al., 2010), were not observed in the present clinical population. The seemingly normative baseline cortisol levels in CVHs may be a consequence of antipsychotic medications (Pruessner et al., 2017), as increased baseline cortisol is primarily observed in medication-naïve psychosis populations (Gunduz-Bruce et al., 2007; Mondelli et al., 2010). Indeed, this may explain why overall cortisol levels in CVHs did not differ compared to HCs, whilst functional GR impairments, discussed below, were much more prevalent. Further, the fact that the clinical population consisted of voice-hearers across diagnostic boundaries may be another reason for differences to studies with samples conducted in schizophrenia patients. The α-amylase levels in CVHs were somewhat surprising, and may partially suggest that stress physiology alterations in CVHs are specific to the HPA axis, but not the ANS.

As hypothesised, CVHs showed greater rates of dexamethasone non-suppression than HCs, at rates congruent with the evidence from systematic reviews (Bradley and Dinan, 2010; Yeragani, 1990). Unexpectedly, however, the findings on dexamethasone non-suppression rates suggest that HVHs may form a middle point between CVHs and HCs in terms on their GR-function. This
pattern is similar to that of the prevalence of stressful life events in the present study, where CVHs showed significantly higher rates than HCs, but HVHs did not differ from either group, and previous studies have implicated adversity exposure in DST non-response (Carpenter et al., 2009). Thus, the partial evidence for impaired GR-function in HVHs may also be related to adversity exposure in this population.

As hypothesised, subjective stress response to the SECPT differed significantly between groups, with higher anticipatory stress appraisals and subjective stress levels in CVHs throughout. Furthermore, they appeared to show no subjective reaction to the SECPT, whereas subjective stress levels in HVHs and HCs decreased following exposure. CVHs also showed similar overall cortisol levels to HCs during the SECPT, yet failed to show the increase in cortisol secretion in response to the stressor, as was observed in HVHs and HCs. This blunted stress response is in line with our hypotheses, as well as with previous meta-analytic evidence in psychosis populations (Ciufolini et al., 2014) and mirrors the one existing study applying the SECPT to a psychosis population (Rubio et al., 2015). However, the hypothesis of exacerbated α-amylase response in CVHs was not supported, with no significant group differences observed. These findings suggest that most HPA-alterations observed in psychosis are also specifically observed in CVHs, whereas the ANS marker utilised here showed no such effects.

An intriguing finding was that HVHs showed lower total cortisol levels during the SECPT than both HCs and CVHs, especially during the initial phases of the SECPT paradigm. Whilst this was not mirrored in their diurnal cortisol levels, this finding nonetheless requires future investigation. There are several studies reporting that childhood (Carpenter et al., 2007; Carpenter, Shattuck, Tyrka, Geracioti, and Price, 2011; Voellmin et al., 2015) as well as lifetime adverse events in healthy individuals (Elzinga et al., 2008; Lovallo, Farag, Sorocco, Cohoon, and Vincent, 2012) are associated with similar HPA stress-reactivity patterns (i.e., reduced cortisol levels in stress paradigms) as those observed in the HVHs in this study. Interestingly, these differences in HPA-activity are independent of subjective stress levels (Voellmin et al., 2015). As
reviewed in Chapters 2 and 4, HVHs have been found to report greater levels of trauma exposure than HCs, and although this difference failed to reach significance in the present study, it may be the most likely explanation for the present finding. It remains unclear whether these HPA alterations (i.e., lower cortisol levels in stress paradigms) constitute a risk factor for the future development of stress-related pathology, or if the decreased HPA activity of trauma-exposed individuals in psychosocial stress paradigms is in fact indicative of resilience (Voellmin et al., 2015). Supporting the resilience hypothesis, the adversity-exposed individuals in these studies, as well as the present study, have no mental health disorders despite trauma exposure. Conversely, Chapter 2 presented evidence of greater risk for mental disorders in HVHs, and the observed HPA-reactivity pattern, as well as the finding on potentially decreased GR function, may partially underlie this vulnerability. Perhaps higher rates of DST non-suppression are also mirrored by the SECPT results, where HVHs showed a slower recovery than HCs, suggesting slower negative feedback in HVHs compared to HCs. Like HCs however, and unlike CVHs, they showed a normative cortisol increase in response to the stress exposure.

As would be expected, group comparisons on questionnaires showed significantly greater depression, anxiety and stress scores in CVHs compared with HVHs and HCs, who did not differ from each other. CVHs also scored lower on trait mindfulness than both HVHs and HCs, in line with previous findings on less mindful voice appraisals in CVH (Peters et al., 2016). CVHs were significantly more likely to have a low SES (indicated by current employment and educational attainments), and were more likely to be socially isolated (as indicated by cohabitation and relationship status). CVHs reported significantly higher rates of total stressful life events than HCs, whereas HVHs did not differ from either HCs or CVHs. For physical abuse CVHs reported significantly higher rates than both HVHs and HCs, who did not differ from each other. Surprisingly, the three sample populations did not differ on any parameters related to substance use, and all showed high rates of exposures to cannabis and amphetamines. Potentially, the
recruitment of participant groups from the urban South London environment, where illicit substances may be more readily available than e.g., rural areas, may explain these high rates.

CVHs and HVHs did not differ in the total anomalous experiences they endorsed on the CAPS, or their intrusiveness, with higher scores in both CVHs and HVHs than in HCs. However, for frequency and distressing impact of anomalous experiences, CVHs scored significantly higher than HVHs, who in turn scored significantly higher than HCs. AVH-specific parameters also differed between CVHs and HVHs, with CVHs showing greater loudness, frequency and distress on the PSYRATS, and later age of onset than HVHs, yet no differences in attribution. CVHs also reported more maladaptive beliefs about and responses to their voices, as indicated by higher malevolence, omnipotence and resistance BAVQ-R scores, and lower benevolence and engagement scores. Furthermore, whilst overall VPDS scores did not differ, CVHs were more likely to perceive their voice as being able to harm them. These findings are broadly in line with the systematic review presented in Chapter 2.

6.4.2 Strengths and Limitations

There are several key strengths to the present study. To the best of the author’s knowledge, this is the first study to characterise HPA alterations specifically in voice-hearers with and without a need for care. Further, this is the first study to characterise the stress-function of HVHs in relation to HCs and CVHs, thus allowing for specific evaluation of the role of stress-function in need for care. Further, very detailed assessments of psychophysiological stress-function were undertaken, and the study employed a symptom-focused design, in line with recent suggestions that this leads to more precise, valid and transferable research findings (Insel et al., 2010).

Moreover, several efforts were also undertaken to ensure validity of findings and pre-empt confounds. There is well documented evidence for lower pain sensitivity in schizophrenia patients (Stubbs et al., 2015), which could potentially impact the stress response during the
However, the inclusion of a social stress component in the present paradigm meant that the stressor was not exclusively pain-dependent. Furthermore, study analyses showed no significant differences in the time CVHs could endure the ice water, suggesting that differential pain sensitivity did not affect the results. Finally, in addition to classical frequentist statistical methods, sensitivity analyses and reporting of effect sizes as well as Bayesian statistics were carried out. Thus, it is possible to assess the power of the present design, and evaluate the magnitude of effects and reliability of statistical results with more detail and confidence.

However, there were also several limitations. It was not possible to measure dexamethasone levels following administration. Nevertheless, Cassidy et al. (2000) showed that the use of a wider time window including several sampling time points over the day minimised confounding risk and meant it was not necessary to measure variance in dexamethasone levels directly. Prior studies have similarly not measured dexamethasone levels (Coryell, Fiedorowicz, Zimmerman, and Young, 2008; Fries et al., 2014; Thompson et al., 2007), giving confidence that the present design was able to detect differences accurately. Similarly, it was attempted to assess for potential effects of different awakening times across groups. Whilst the data indicated no such differences, the self-report at home was nonetheless patchy and not all participants recorded their awakening time.

Sample characteristics suggest at least partial matching, including for age and ethnicity, but not for gender, the confounding effect of which cannot be ruled out. Sample sizes further slightly differed between groups and stress measures, potentially leading to some statistical noise in the present findings. All CVHs in the present study were medicated, with second generation antipsychotic and clozapine treatment in 85% of CVHs. As noted in the literature on psychosis and HPA-function (Pruessner et al., 2017), antipsychotic medications, particularly atypical antipsychotics, impact on cortisol levels. Thus, it is possible that some of the findings on HPA-function in CVHs in the present study, particularly those concerning overall cortisol levels and SECPT reaction, were skewed by antipsychotic treatment, and may not be specific to AVHs or
need for care. Due to the small sample size of this study, it was not possible to covary for the effect of medication use, or other potential confounders such as gender or BMI.

Whilst efforts were made to characterise the study samples on several relevant variables identified by Chapter 3, Chapter 4 and Chapter 5, such as substance misuse, beliefs about voices and life events, the potential moderating and/or mediating effects of these variables could not be explored. Due to the limited sample size, it was not possible to apply more complex statistical procedures that could reveal structural relationships between such variables and the stress parameters assessed. Such analyses may have clarified some of present findings, most notably the reasons behind the lower overall cortisol levels in HVHs during the SECPT, which can presently only be speculated about. Further, the small sample sizes limit the interpretability of study findings and their relation to the extant literature. For example, the role of trauma exposure is likely to affect the relationship between need for care, AVHs and stress measures in the present study, however it was not possible to test for such an effect with adequate power.

The lack of plasma biomarker data in the present study meant it was not impossible to assess the association of cortisol in blood and saliva to determine a study-specific cut-off value for classifying dexamethasone non-suppressors. In relation to this, the home sampling procedures utilised in the present project may be suboptimal in ensuring compliance with saliva sampling procedures, which has been shown to impact sample quality in previous research (Broderick et al., 2004). However, several steps were undertaken to maximise compliance, including reminder phone calls, careful and repeated instructions, the use of a time window the DST as well as exclusion of outliers in the statistical analyses.

By only considering the salivary markers cortisol, for the HPA axis, and a-amylase, for the autonomic nervous system, the assessment of stress-function in the present study was limited. Especially a-amylase, a somewhat novel marker that has not yet been fully characterised yet (Nater et al., 2006; Rohleder et al., 2004), may not be sufficient to investigate ANS function
comprehensively. Rather, heart rate variability, respiratory rate and/or plasma adrenaline measurements would be necessary to get a more complete picture of ANS function specific to AVHs and need for care. Similarly, whilst great care was undertaken to assess different aspects of HPA activity, including morning and baseline activity, stimulated activity and negative feedback capacity, all of these measures have their limitations. Previous studies have used higher numbers of samples to assess diurnal cortisol patterns, and often sampled for several days to decrease the impact of outlier data. Some studies have further utilised 24h-urine measurements of cortisol, or hair cortisol, for more accurate assessments of short- and long-term cortisol secretion. Similarly, the cortisol awakening response is often characterised using several sampling time points over the first hour post-awakening. Further, whilst the dexamethasone suppression test is suggestive of impaired GR feedback, the molecular mechanisms remain unclear unless other assessments, such as genetic and epigenetic investigations, are also undertaken.

6.4.3 Implications and Future Directions

Several important clinical and research implications can be drawn from the present study. First, the present data suggest that stress-function differs depending on the need for care of voice-hearers. Future longitudinal research is needed to assess whether the stress response is a marker of resilience in HVHs. The lower cortisol levels of HVHs during the SECPT could be related to wider stress resilience of the HPA axis, which could explain the non-clinical status. Further, it should be evaluated to which degree a change in need for care, i.e., therapeutic response to psychological or pharmacological treatments, is also associated with normalisation of stress-function. In depression, there is evidence that GR function is normalised through antidepressant treatments (Anacker et al., 2011), and early evidence in PTSD suggests normalisation of FKBP5 mRNA expression is associated with treatment response to CBT (Levy-Gigi, Szabó, Kelemen, and Kéri, 2013). Potentially, treatment approaches that alleviate voice-distress subjectively may
partially do so through physiological adaptations. The present evidence suggests that antipsychotic medication alone is not sufficient to restore GR function.

Second, there is some evidence to suggest the DST could be valuable as a risk assessment tool in populations presenting with AVHs. To explore this potential, future longitudinal research should assess GR-function in at-risk populations as well as adolescent samples presenting with AVHs, and determine whether impaired GR-function is a predictor of later need for care. Notably, previous research in depression has suggested that the presence of childhood traumatic experiences may skew Dex/CRH test specificity and diminish its potential as a biomarker to identify depressed endophenotypes, despite being initially hailed as such (Carpenter, Ross, et al., 2009). Given that the gradients of adversity exposure (CVH > HVH > HC) are similar to that of dexamethasone non-response (CVH > HVH > HC), a similar effect could apply here. To assess this, future research should obtain larger sample sizes as well as more comprehensive HPA and adversity exposure assessments. Similarly, the confounding effects of antipsychotic treatment on HPA-function, particularly baseline cortisol and acute reactivity, can only be controlled for through the recruitment of medication-naïve or at least currently unmedicated CVH participants.

Third, a more comprehensive HPA assessment in CVHs and HVHs is needed to outline the functional and aetiological implications of the present research. Genetic risk alleles related to HPA function, and their interactions with and modulation by early life adversity, e.g., through epigenetic adaptations, are implicated in aberrant HPA activity as well as schizophrenia (Daskalakis and Binder, 2015; Palma-Gudiel, Córdova-Palomera, Leza, and Fañanás, 2015; Sinclair, Fullerton, Webster, and Weickert, 2012). Several genes related to GR function, including N3RC1, the glucocorticoid receptor gene, and its promoter regions, as well as FKBP5, the chaperone protein that binds cytosolic GR and modulates transportation to the nucleus, are valuable markers to understand both GR function as well as patterns of HPA-reactivity (Daskalakis and Binder, 2015; Palma-Gudiel et al., 2015; Sinclair et al., 2012). Given the strong...
association of AVHs with adversity exposure, as well as the evidence of HPA dysregulation presented here, these molecular markers should be investigated further in relation to AVHs and need for care. Similarly, more detailed analyses of functional HPA and ANS alterations should be undertaken to further increase a) the confidence in the present findings and b) the knowledge about functional relationships between individual assessments, e.g. GR function and acute reactivity. This could include: a) more detailed assessment of subjective and physiological stress-reactivity through the use of more psychosocial (e.g., Montreal Imaging Stress Test; Dedovic et al., 2005) or more physiological (e.g., CO2 challenge; van Duinen, Schruers, Maes, and Griez, 2005) stressors, b) the use of more sampling time points and days to decrease statistical noise, c) the assessment of more long-term HPA-function including hair and 24h-urine cortisol, and d) more detailed assessment of ANS function including respiratory rate, heart rate variability and plasma adrenaline. The collection of such data in large samples could, in combination with psychosocial interview assessments as those carried out here, lead to the ability to use more complex statistical methods, e.g., structural equation models, that can help inform about the precise interrelationships of psychological and physiological stress-function.

Fourth, the association of specific HPA-activity patterns with other biomarkers implicated in need for care need to be investigated. The dopamine hypothesis proposes that elevated dopaminergic activity in the striatum underlies aberrant salience of unwarranted stimuli and associations between such stimuli, which then causes the formation of delusional explanations and beliefs (Howes and Kapur, 2009; Kambeitz, Abi-Dargham, Kapur, and Howes, 2014). As demonstrated by Howes et al. (2013), HVHs do not present with the upregulated dopamine synthesis capacity seen in psychosis patients. The mesolimbic dopamine system is highly responsive to glucocorticoid secretion (Marinelli and Piazza, 2002), and several studies have demonstrated that acute psychosocial stress leads to increased regional dopamine signalling (Hernaus et al., 2015; Mizrahi et al., 2014; Nagano-Saito et al., 2013; Pruessner, Champagne, Meaney, and Dagher, 2004; Vaessen, Hernaus, Myin-Germeys, and van Amelsvoort, 2015).
Interestingly, Mizrahi et al. (2012) have reported that medication-naïve schizophrenia patients and individuals at clinical high-risk have significantly greater dopaminergic responses to psychosocial stress than healthy controls. Investigating the stress-dopamine link in CVHs and HVHs may further explain pathophysiological adaptations associated with need for care, the link between AVHs and delusional ideation, as well as the impact such a link may have on psychological sequelae, such as beliefs about voices. Indeed, perhaps the most difficult task for future research will be to integrate psychological and physiological findings. For some ANS markers, such as HRV, a clear link to emotion regulation has been demonstrated (Holzman and Bridgett, 2017). Future research should assess to which degree psychological differences in CVHs and HVHs, such as cognitive responses to and appraisals of voices are related to stress physiology. For example, CVHs undergoing cognitive behavioural therapy could be assessed on stress biomarkers as well as key psychological variables, to then investigate whether markers correlate in their treatment response.

6.4.4 Conclusions

The present study demonstrates significant alterations to the stress physiology of clinical and healthy voice-hearers, with significant differences depending on need for care. Specifically, our research is the first to demonstrate that HPA-function is specifically implicated in the pathophysiology of CVHs. However, against our expectations, HVHs showed HPA-patterns divergent from HCs, raising the interesting possibility of specific resilience markers. Activity of the ANS has not been implicated in the present study. Future research needs to be undertaken to explore the functional, psychological, aetiological and predictive implications of these findings in greater detail.
Chapter 7 – Discussion

7.1 Findings

The present doctoral project revealed several key findings to add to the extant literature on auditory verbal hallucinations (AVHs), psychosis and stress, presented in Table 7.1.

In Chapter 4, the potential developmental impact of adversity exposure on need for care was evaluated in the context of a 3-Hit conceptualisation (Daskalakis et al., 2013). The findings provided evidence for differential adversity exposure in CVHs and HVHs in adolescence and adulthood (Hit 3), as well as greater familial risk (Hit 1). In line with the hypotheses, HVHs and CVHs did not differ in adversity exposure in childhood (Hit 2). However, CVHs were more likely than HVHs to have fewer years in education, and more exposure to cannabis and other substance use. Contrary to expectations, victimisation and discrimination experiences in Hit 3 did not differ between the groups, suggesting that developmental timing and repeated victimisation exposure may be less important in leading to a need for care than exposure to different, or specific, types of adversity. Unlike previous findings (van Lutterveld et al., 2014), CVHs were more likely to have family members with a history of psychosis, although history of other disorders did not differ between CVHs and HVHs. Family history of psychosis, fewer years in education, and non-cannabis substance use predicted perceived stress after controlling for group, suggesting that several of the specific types of adversity that CVHs are more exposed to are also those driving perceived stress. Thus, this study extended the existing evidence on familial risk and adversity exposure in CVHs and HVHs detailed in Chapter 2, identified key variables that differentiate CVHs and HVHs, and therefore AVHs and need for care, and may contribute to the stress-sensitivity of CVHs.
### Table 7.1 – Key findings of each experimental study

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Key Findings</th>
</tr>
</thead>
</table>
| **Chapter 4 - Need for care, adversity exposure and perceived stress in clinical and healthy voice-hearers** | - The 3-Hit model is a useful framework within which to assess the impact of adversity on need for care in voice-hearers  
  - Victimisation and discrimination exposure do not differ significantly in CVHs and HVHs, in childhood (Hit 2) or adolescence/adulthood (Hit 3), neither do childhood socio-economic status or family history of non-psychotic mental disorders  
  - Substance misuse and years in education, as well as family history of psychosis, differ significantly between CVHs and HVHs  
  - These variables are predictive of perceived stress after controlling for group |
| **Chapter 5 - The effects of voice content and mindful appraisals on stress-reactivity in a voice analogue study** | - Voice content may be a crucial driver of differential, subjective stress-reactivity in CVHs and HVHs  
  - Voice content does not seem to impact on salivary stress markers  
  - Mindful appraisals of voices are associated with a lessened stress response, although negative content also decreased mindful appraisals |
| **Chapter 6 - Psychophysiological Stress-Function in Clinical and Healthy Voice-hearers** | - CVHs have a diminished, rather than an increased, awakening cortisol response compared to both HVHs and HCs, who do not differ from each other  
  - Basal cortisol levels do not differ between groups  
  - CVHs show a significantly blunted dexamethasone response compared to HCs, whereas HVHs seem to form a middle point between the groups  
  - CVHs show greater subjective stress levels throughout the SECPT, greater anticipatory stress appraisals, and greater perceived stress levels in the previous week, than HVHs and HCs, who do not differ from each other |
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• CVHs have a blunted cortisol response to the SECPT, while HVHs showed the same response as HCs</td>
</tr>
<tr>
<td></td>
<td>• HVHs have a normative HPA response, but lower cortisol throughout the SECPT, than both CVHs and HVs</td>
</tr>
<tr>
<td></td>
<td>• CVHs, HVHs and HCs do not differ on diurnal or SECPT-stimulated α-amylase levels</td>
</tr>
</tbody>
</table>
Chapter 5 investigated whether negative voice content between CVHs and HVHs exacerbate stress-reactivity in an analogue study using simulated voices in healthy individuals with no AVHs. For this purpose, a novel voice simulation paradigm was developed, utilising the reports of clinicians and voice-hearers to establish valid and reliable stimuli, as well as precise matching of word frequencies, narrators and timing of voices across conditions with different voice content. Negative simulated voices exacerbated the subjective stress response to the Montreal Imaging Stress Task compared to neutral voices and ambient sounds, which did not differ from each other. However, there was no effect of voice-content on cortisol or α-amylase levels. There are two potential reasons for these discrepant findings. First, it is feasible that voice-content is unrelated to potential differences in HPA- and ANS-function of HVHs and CVHs. Alternatively, it is possible that the subjective stress response has subtler and more sensitive gradings than the physiological response. Nonetheless, the large effect of negative voice content on the subjective stress response may drive differential stress-reactivity in CVHs, compared to HVHs. Consistent with evidence from trials of mindfulness for clinical voice-hearers, which showed reduced voice distress following therapy (Chadwick et al., 2016, 2009; López-Navarro et al., 2015; Shawyer et al., 2007), a mindful stance towards the voices during the paradigm was associated with lower subjective stress levels. However, exposure to negative voice content was in turn related to lower mindfulness, suggesting that the capacity for mindful voice-appraisals may be diminished by negative voice content. Building on the evidence identified in Chapter 2, this study provides experimental evidence to show that voice-hearing in itself may not be problematic; rather it is the negative voice content that leads to pathological outcomes, such as increased subjective stress and reduced capacity for mindful voice-appraisals, and may therefore drive need for care.

Finally, Chapter 6 investigated the role of psychophysiological stress-function in the impact of AVHs on need for care. As reviewed in Chapter 3, there is substantial evidence to suggest that psychosis is closely linked with stress-exposure, -reactivity and -physiology. Childhood trauma
elevates psychosis risk and sensitises to stress exposure in later life. Both major branches of the physiological stress system appear altered in psychosis patients (Montaquila et al., 2015; Pruessner et al., 2017), suggesting that subjective changes in stress-function are accompanied by allostatic load. However, despite the evidence on childhood trauma and AVHs, as well as childhood trauma and dysregulated stress-function, stress-function has not been investigated in voice-hearers specifically.

To address this gap, CVHs, HVHs and HCs were compared on key measures identified by the psychosis stress literature reviewed in Chapter 3. This comprehensive assessment of psychophysiological stress-function included basal and stimulated hypothalamic-pituitary-adrenal (HPA) and autonomic nervous system (ANS; assessed via α-amylase) activity, and subjective stress levels. Further, key variables identified in Chapter 2 and Chapter 3 were assessed, including voice phenomenology, beliefs about voices, mood disturbance, trait mindfulness, substance use, and exposure to stressful life events. Group differences on voice phenomenology, mood disturbances, trait mindfulness, anomalous experiences and exposure to stressful life events were broadly in line with the literature reviewed in Chapter 2 and findings from Chapter 4, although substance use did not differ between groups.

Compared to both HVHs and healthy controls (HCs), CVHs showed diminished awakening cortisol levels as well as impaired negative HPA feedback capacity, as assessed by the Dexamethasone Suppression Test. Furthermore, they reported significantly greater subjective stress levels throughout the Socially Evaluative Cold Pressor Test (SECPT), greater anticipatory stress appraisals, and greater perceived stress levels in the week before assessment than the other two groups, who did not differ from each other. Unlike HVHs and HCs, the CVHs also showed a blunted cortisol response to the SECPT. Unexpectedly, HVHs showed significantly lower cortisol levels than both CVHs and HCs throughout the task, while they were in between the other two groups in terms of their negative HPA feedback capacity. No significant group
differences were found for basal diurnal cortisol or α-amylase, or SECPT α-amylase response. Thus, study indices of HPA-function but not ANS-function in CVHs is congruent with findings reported in the wider stress and psychosis literature presented in Chapter 3, and may contribute to differential need for care of CVHs and HVHs. Indeed, it may be possible that the lower cortisol levels in HVHs during the SECPT hint towards a resilience mechanism in this population.

7.2 Strengths and Limitations

The present project had several key strengths. First, the individual studies presented here are novel in their contribution to the field of stress research in the psychosis continuum. Second, the thesis employed a symptom-focussed approach, thereby ensuring that findings apply specifically to AVHs and help understand this particular symptom, as opposed to previous research that relied on the diagnostic schizophrenia classification combining different symptoms and experiences. Third, the research utilised HVHs as a comparison population; they are unique in the potential to help research determine whether findings in CVHs relate to the experience of AVHs, or need for care. Fourth, a range of methodological approaches were undertaken, including cross-sectional and experimental paradigms, as well as self-report and physiological measures. Whilst the studies comparing HVHs and CVHs thus allowed for direct testing in target populations, the use of an experimental paradigm provides a way to test the theoretical implications voice content may have in stress-reactivity, which cannot be tested otherwise. Similarly, the use of biological and psychological measures, as well as measures of social adversity, provides a way to integrate and compare the stress research data in the context of a biopsychosocial framework. Last, for all data chapters sensitivity analyses and reporting of effect sizes as well as Bayesian statistics were carried out, in addition to classical frequentist statistical methods. This strategy made it possible to assess the power of the studies, and evaluate the magnitude of effects, reliability and relative likelihood of statistical results with more detail and confidence.
However, there are also several limitations to the studies reported in this thesis. Notably, due to the time and budgetary restraints of a doctoral thesis, few of the studies presented here were carried out with designs that allow for inference of causal relationships. All studies consist entirely of cross-sectional research. Whilst some of the literature presented in Chapter 3, most notably that on childhood trauma, suggests that adversity exposure increases psychosis risk, it remains impossible to assess whether the identified factors, such as voice content, differential adversity exposure or altered stress physiology, are simply epiphenomena of pathology. Similarly, small sample sizes may have contributed to some of the inconsistent findings between individual chapters, most notably the divergent findings on substance misuse in Chapter 4 and Chapter 6, as well as the findings of increased familial risk in HVHs reported on in Chapter 2 and not replicated in Chapter 4. This smaller sample size may have further confounded the ability of the present study to generalise the findings to wider, more divergent voice-hearer populations (e.g., medication-naïve CVHs), and likely decreased the power to adequately covary for confounding variables.

Further limitations are related to the validity of several measures and experimental methods. In Chapter 4, several variables, including substance misuse and socioeconomic status, as well as genetic loading, lacked the detail of the adversity exposure assessment. Specifically, the validity of the proxies for socioeconomic status and genetic loading may have suboptimal measurement validity, whilst age ranges were not available for substance use. The voice simulation utilised in Chapter 5 necessarily only approximates the experience voice-hearers may have, but is unlikely to lead to the same impact or appraisals as in actual voice-hearers. Similarly, the stress tasks in both Chapters 5 and 6 are laboratory stressors, which, whilst effective in eliciting psychophysiological responses, are unlikely to reflect stressful experiences commonly experienced in daily life of psychosis patients. Particularly interpretation of SECPT findings is affected by this ecological limitation. Further, whilst dexamethasone response does reflect GR-
responsiveness, HPA activity also involves activity of the mineralocorticoid receptor (MR), which is activated by cortisol but not dexamethasone. There is some evidence for negative feedback mechanisms involving the MR (Atkinson et al., 2008), and thus dexamethasone potentially represents a quite artificial induction of negative feedback in the HPA axis. Some of the measures employed in HVHs and CVHs may also be impacted by factors variables relating to clinical status, such as the potential effect of illness onset on years in education in Chapter 4, and the effects of antipsychotic on stress physiology in Chapter 6.

### 7.3 Implications and Future Directions

Several implications for clinical treatment and future research can be drawn from the present project.

Whilst some gaps identified in Chapter 2 were addressed in the present thesis, several others remain to be taken up by future research. For more precise assessments of AVH phenomenology, mental health risk, social support structures as well as developmental pathways, large epidemiological and longitudinal research designs are necessary. To assess the long-term impact of voice-hearing on mental health risk, a cohort of young adolescents should be assessed for presence of voices as well as phenomenology of voices and then followed over several decades to identify variables that can determine mental health risk and aid early intervention. Putatively, presence of social support may also shape more benevolent outcomes as opposed to circumstances where such social structures are lacking. Particularly the fact that these individuals are frequently recruited from spiritualist groups suggests that voice-hearing in a context where such experiences are encouraged and shared may be associated with less risk of mental health difficulties, and this should be investigated further. The inclusion of less dichotomised samples, such as voice-hearing populations that have transitioned from or to need for care, would also be helpful in determining variables specific to need for care, and variables
specific to AVHs. Specifically, factors like voice content, relationship to voices or stress-function
could potentially change over time for better or worse, and it would be useful to know whether
a) such changes precede onset of or recovery from clinical status and b) can be modulated to
facilitate recovery. Further, this would provide more detail on the psychosis continuum
framework.

The evidence in Chapter 4 should be built upon in epidemiological population studies to explore
the role of adversity exposure in more diverse voice-hearing samples, and assess potential
additive or interaction effects of adversity types. Evidence from a 10-year prospective cohort
study showed that early exposure to adversity increased the risk of adversity exposure in
adolescence, which in case of recent severe adversity, interacted additively to increase the risk
of psychosis (Lataster et al., 2012). Similar relationships could be present in determining
outcome of AVHs and should be investigated using similar designs as that of Lataster and
colleagues (2012). More valid measures of genetic risk, such as heritability, genome-wide
association or molecular genetic studies, socioeconomic status, and more detailed assessment
of substance misuse should also be carried out. The timing of substance misuse differentially
affects psychosis risk, with a greater risk effect of adolescent as opposed to adult use (Arseneault
et al., 2002). Similarly, early cannabis use has a greater effect of HPA dysregulation that later
onset (Huizink et al., 2006), and future research should take such effect into account. Similarly,
the present study, and all existing literature on HVH familial risk, used family incidence of mental
illness as a marker of genetic loading. However, evidence suggests an interaction of FKB5
polymorphisms and childhood trauma in increasing risk for psychotic symptoms and HPA
dysregulation (Collip et al., 2013a). Such interaction effects can only be sensibly investigated
using specific genetic markers. Further, the chapter highlights the importance of adversity types
that could be malleable to social interventions, including substance misuse and continuing
education, which should be explored further in prodromal psychosis intervention research.
Whilst Chapter 5 suggested no effect of voice-content on stress physiology, the potential association of voice-content with stress physiology in HVHs and CVHs should nonetheless be investigated. Future research should also investigate the predictive value of negative voice content in transition rates of at-risk populations. In line with the hypothesised effect of stress exposure on dopaminergic dysregulation, and subsequent delusional ideation, the effect of simulated voices on state paranoia should also be assessed in future research. Putatively, negative voice content may drive maladaptive appraisals and foster paranoid ideation. Finally, future research should address experimentally whether purposefully employed mindful response styles to voices also attenuate stress-reactivity, whether mindful response styles are simply more prevalent in individuals with greater stress resilience, or both.

Several important clinical and research implications can be drawn Chapter 6. First, it should be evaluated to which degree a change in need for care, i.e., therapeutic response, is also associated with normalisation of stress-function. To investigate whether normalisation of stress-function mediates clinical improvements, psychophysiological stress-measures should be included in trials of psychological interventions shown effect in psychosis and AVHs such as cognitive-behavioural therapy (Burns, Erickson, and Brenner, 2014; Turner, van der Gaag, Karyotaki, and Cuijpers, 2014) or mindfulness interventions (Chadwick et al., 2016; Strauss, Thomas, and Hayward, 2015). Similarly, the identification and assessment of therapeutic methods that could aid normalisation of dysregulated stress-function, such as heart rate variability training for the autonomic nervous system, should be addressed in future clinical research. Second, future longitudinal research should assess GR-function in at-risk populations as well as adolescent samples presenting with AVHs, to determine whether impaired GR-function is a predictor of later need for care. Third, the confounding effects of antipsychotic treatment on HPA-function can only truly be controlled for through research in medication-naïve CVH participants. Fourth, a more comprehensive HPA and ANS assessment in CVHs and
HVHs, including more detailed and varied sampling methods (e.g., hair cortisol or heart rate variability), assessment of risk alleles and gene environment interactions, is needed to specify the functional and aetiological implications of altered stress-function in CVHs and HVHs. Fifth, the collection of such data in large samples could aid more complex statistical methods in highlighting the precise interrelationships of psychological and physiological stress-function, and help understand the finding of lower SECPT cortisol in HVHs.

Finally, the association of specific HPA-activity patterns with dopaminergic activity need to be investigated in the context of AVHs. The mesolimbic dopamine system is highly responsive to glucocorticoid secretion (Marinelli and Piazza, 2002), and several studies have demonstrated that acute psychosocial stress leads to increased regional dopamine signalling as measured by positon emission photography (Hernaus et al., 2015; Mizrahi et al., 2014; Nagano-Saito et al., 2013; Pruessner, Champagne, Meaney, and Dagher, 2004; Vaessen, Hernaus, Myin-Germeys, and van Amelsvoort, 2015). Interestingly, Mizrahi et al. (2012) have reported that medication-naïve schizophrenia patients and individuals at clinical high-risk have significantly greater striatal dopaminergic responses to psychosocial stress than healthy controls. In line with these findings, Howes and colleagues (2016) have recently proposed a stress feedback model whereby stress contributes to dopaminergic dysregulation, which in turns leads to increased formation of delusions and aberrant salience, which then leads to increased distress and need for care. Assessing the effects of psychosocial stress on HPA-reactivity and dopamine signalling in CVHs and HVHs may further elaborate whether the link of HPA and dopamine activity explains the differential need for care.

### 7.4 Conclusion

The present PhD project contributed to current knowledge of the relationships between stress-function, distress and adversity in the experience of voice-hearing individuals with and without
need for care. CVHs demonstrate several alterations in their stress physiology, including blunted reactivity to stress and impaired negative feedback, which appear uniquely linked to need for care, rather than AVHs in general. The inclusion of HVHs in this research project has allowed us to identify several developmental (e.g., substance misuse), experiential (i.e., voice content), psychological (e.g., voice appraisals) as well as physiological (i.e., HPA-reactivity) variables that may explain the resilience of HVHs, as well as need for care of CVHs. Future research will need to further explore whether and how these differences are related to the aetiology and maintenance of need for care, and whether their modulation through therapeutic strategies can be applied in clinical practice.
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Appendices

Appendix I – PNM RESC Ethics

David Baumeister
Room 4.04
Addiction Sciences Building

Institute of Psychiatry, Psychology and Neuroscience
King’s College London
London SE5 8BB

18 March 2015

Dear David,

PNM/14/15-111 Effects of auditory stimuli on physiological reaction to mental demands

Review Outcome: Approved pending amendments/clarifications

Thank you for submitting the above application which the PNM RESC considered at our meeting on 17 March 2015. I am writing to advise you that there have been some issues raised with your application which require addressing before full approval is granted. As such you will need to respond to each of the below comments accordingly, as well as making any requested changes to the relevant sections of the application form:

Issues raised (must be addressed in order for approval to be granted):

1. Section 7.1: The Committee recommends that participants are allowed at least 24 hours to consider whether to take part.
2. Section 7.2 and Information Sheet: Specify a date as the deadline for withdrawal of participant data.
3. Section 10e: Provide a departmental postal address for the location at which research data will be stored after the study.
4. Information Sheet:
   i. Clarify that the study is being conducted for a PhD at King’s College London.
   ii. Remove the paragraphs entitled ‘Complaints and Harm’.
   iii. Remove the paragraph starting: ‘If you would like to speak to someone regarding independent advice...’
   iv. Replace both occurrences of ‘King’s College London Ethics Committee’ with ‘Psychiatry, Nursing and Midwifery (PNM) Research Ethics Subcommittee (RESC) at King’s College London’.
   v. Insert the paragraph starting ‘If this study has harmed you in any way...’ before the contact details for your academic supervisor.
   vi. Use current KCL logo.
5. Posters: Use current KCL logo

6. Consent Form:
   i. Use the current KCL logo.
   ii. Be sure to include all required bullet points and any suitable bullet points found on the KCL template Consent Form.

7. Section 6.3: The Committee assumes that all recruitment methods it will be incumbent on participants to contact you in the first instance.

Recommendations (it is not essential that these are addressed but the reviewing Committee consider that these changes would improve your research. You are not required to provide feedback on these points):

8. Sections 2.2 and 2.3: Please note that ethical approval for PhD studies is normally granted for a period of three years.

Please email the revised sections of the application form, with all changes highlighted for ease of review, and a cover letter detailing the changes made to the PNM RESC inbox pnm@kcl.ac.uk for review and approval. Your supervisor must be copied in on the email submission to provide assurance that they have authorised the amendments which you have made.

The covering letter and the requested amendments/clarifications can be submitted to the Research Ethics Office, via email, at any time as these do not need to go for full review to the PNM RESC, but will usually be reviewed by Chair's action.

Please note that you should use your reference number (given in the title of this letter before the study name) on the recruitment literature (including the Information Sheet and any consent form) and in all future correspondence with us regarding this application.

If for some reason you choose not to proceed with this research ethics application, please inform the Research Ethics Office accordingly.

Please note that research involving human participants must not commence until full ethical approval has been granted.

Yours sincerely,

James Patterson, Senior Research Ethics Officer
For and on behalf of
Professor Gareth Barker, Chairman
Psychiatry, Nursing and Midwifery Research Ethics Subcommittee (PNM RESC)

Cc. Emmanuelle Peters
## Appendix II – Voice Simulation Scripts

<table>
<thead>
<tr>
<th>Time (m:s)</th>
<th>Voice</th>
<th>NEG</th>
<th>NEU</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.04</td>
<td>F1</td>
<td>Can't do anything right</td>
<td>Come and see</td>
</tr>
<tr>
<td>0.11</td>
<td>M1</td>
<td>Don't do that</td>
<td>Make me proud</td>
</tr>
<tr>
<td>0.12</td>
<td>M2</td>
<td>What a waste of space</td>
<td>They do it now</td>
</tr>
<tr>
<td>0.17</td>
<td>F1</td>
<td>Hey idiot</td>
<td>Same thing</td>
</tr>
<tr>
<td>0.18</td>
<td>F2</td>
<td>Coward</td>
<td>Morning</td>
</tr>
<tr>
<td>0.19</td>
<td>F1</td>
<td>Stupid</td>
<td>Later</td>
</tr>
<tr>
<td>0.2</td>
<td>F2</td>
<td>Stupid</td>
<td>Later</td>
</tr>
<tr>
<td>0.23</td>
<td>M2</td>
<td>Shame on you</td>
<td>You will return</td>
</tr>
<tr>
<td>0.29</td>
<td>M1</td>
<td>They all know</td>
<td>They do it now</td>
</tr>
<tr>
<td>0.3</td>
<td>M1</td>
<td>See how they look at you</td>
<td>They take the medicine</td>
</tr>
<tr>
<td>0.31</td>
<td>F2</td>
<td>Repulsive</td>
<td>Maybe</td>
</tr>
<tr>
<td>0.32</td>
<td>M1</td>
<td>They are laughing at you</td>
<td>They do what they're told</td>
</tr>
<tr>
<td>0.33</td>
<td>F1</td>
<td>Repulsive</td>
<td>Maybe</td>
</tr>
<tr>
<td>0.34</td>
<td>M2</td>
<td>Worthless</td>
<td>Alright</td>
</tr>
<tr>
<td>0.42</td>
<td>M2</td>
<td>You're losing it</td>
<td>You are coming</td>
</tr>
<tr>
<td>0.43</td>
<td>M1</td>
<td>Crazy</td>
<td>Spring</td>
</tr>
<tr>
<td>0.44</td>
<td>F2</td>
<td>You're really a mess</td>
<td>You look like them</td>
</tr>
<tr>
<td>0.53</td>
<td>F1</td>
<td>Wrong</td>
<td>Right</td>
</tr>
<tr>
<td>0.54</td>
<td>M2</td>
<td>No good</td>
<td>Same thing</td>
</tr>
<tr>
<td>0.55</td>
<td>F2</td>
<td>Wrong</td>
<td>Right</td>
</tr>
<tr>
<td>0.55</td>
<td>M1</td>
<td>Mistake</td>
<td>Spring</td>
</tr>
<tr>
<td>1.02</td>
<td>F2</td>
<td>Give up</td>
<td>Be careful</td>
</tr>
<tr>
<td>1.08</td>
<td>M1</td>
<td>Should be ashamed</td>
<td>Wait and see</td>
</tr>
<tr>
<td>1.09</td>
<td>F1</td>
<td>Shame on you</td>
<td>You will return</td>
</tr>
<tr>
<td>1.09</td>
<td>F2</td>
<td>Shame on you</td>
<td>You will return</td>
</tr>
<tr>
<td>1.15</td>
<td>M1</td>
<td>Hey idiot</td>
<td>Hello</td>
</tr>
<tr>
<td>1.18</td>
<td>M1</td>
<td>Hey idiot</td>
<td>Hello</td>
</tr>
<tr>
<td>1.19</td>
<td>M1</td>
<td>Hey idiot</td>
<td>Hello</td>
</tr>
<tr>
<td>1.2</td>
<td>M2</td>
<td>Hey idiot</td>
<td>Hello</td>
</tr>
<tr>
<td>1.21</td>
<td>F2</td>
<td>Hey idiot</td>
<td>Hello</td>
</tr>
<tr>
<td>1.28</td>
<td>F1</td>
<td>Look how ugly you are</td>
<td>Now you're going out of the door</td>
</tr>
<tr>
<td>1.34</td>
<td>M2</td>
<td>Not good enough</td>
<td>The right thing</td>
</tr>
<tr>
<td>1.41</td>
<td>F1</td>
<td>Everyone hates you</td>
<td>You look like them</td>
</tr>
<tr>
<td>1.42</td>
<td>F1</td>
<td>Go away</td>
<td>Be careful</td>
</tr>
<tr>
<td>1.43</td>
<td>F2</td>
<td>Go away</td>
<td>Be careful</td>
</tr>
<tr>
<td>1.44</td>
<td>F1</td>
<td>Give up</td>
<td>Give it to us</td>
</tr>
<tr>
<td>1.45</td>
<td>F2</td>
<td>Better disappear</td>
<td>Wait and see</td>
</tr>
<tr>
<td>1.46</td>
<td>M2</td>
<td>Go away</td>
<td>Be careful</td>
</tr>
<tr>
<td>1.47</td>
<td>M1</td>
<td>Give up</td>
<td>Wait and see</td>
</tr>
<tr>
<td>Time (m:s)</td>
<td>Voice</td>
<td>NEG</td>
<td>NEU</td>
</tr>
<tr>
<td>-----------</td>
<td>-------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>1.48</td>
<td>M1</td>
<td>Don't do that</td>
<td>Give it to us</td>
</tr>
<tr>
<td>2.03</td>
<td>M1</td>
<td>Can't do anything right</td>
<td>Come and see us</td>
</tr>
<tr>
<td>2.14</td>
<td>F2</td>
<td>Coward</td>
<td>Morning</td>
</tr>
<tr>
<td>2.15</td>
<td>F2</td>
<td>Can't do anything right</td>
<td>Come and see us</td>
</tr>
<tr>
<td>2.23</td>
<td>M2</td>
<td>Loser</td>
<td>Alright</td>
</tr>
<tr>
<td>2.24</td>
<td>M1</td>
<td>Loser</td>
<td>Alright</td>
</tr>
<tr>
<td>2.25</td>
<td>M2</td>
<td>Loser</td>
<td>Alright</td>
</tr>
<tr>
<td>2.26</td>
<td>M1</td>
<td>Loser</td>
<td>Alright</td>
</tr>
<tr>
<td>2.27</td>
<td>M2</td>
<td>Loser</td>
<td>Alright</td>
</tr>
<tr>
<td>2.39</td>
<td>M2</td>
<td>Everyone hates you</td>
<td>You remain silent</td>
</tr>
<tr>
<td>2.46</td>
<td>M1</td>
<td>Not good enough</td>
<td>The right thing</td>
</tr>
<tr>
<td>3.05</td>
<td>M1</td>
<td>Fraud</td>
<td>Spring</td>
</tr>
<tr>
<td>3.06</td>
<td>F2</td>
<td>They all know</td>
<td>They do it now</td>
</tr>
<tr>
<td>3.11</td>
<td>M2</td>
<td>They are laughing at you</td>
<td>You look like them</td>
</tr>
<tr>
<td>3.22</td>
<td>M2</td>
<td>Worthless</td>
<td>Maybe</td>
</tr>
<tr>
<td>3.24</td>
<td>M1</td>
<td>Worthless</td>
<td>Maybe</td>
</tr>
<tr>
<td>3.25</td>
<td>F2</td>
<td>Stupid</td>
<td>Later</td>
</tr>
<tr>
<td>3.26</td>
<td>F1</td>
<td>Worthless</td>
<td>Maybe</td>
</tr>
<tr>
<td>3.37</td>
<td>M1</td>
<td>Go away</td>
<td>Be careful</td>
</tr>
<tr>
<td>3.38</td>
<td>M2</td>
<td>Give up</td>
<td>That's yours</td>
</tr>
<tr>
<td>3.45</td>
<td>F2</td>
<td>Look how ugly you are</td>
<td>Now you're going out of the door</td>
</tr>
<tr>
<td>3.46</td>
<td>M2</td>
<td>Should be ashamed</td>
<td>Come and see us</td>
</tr>
<tr>
<td>4.02</td>
<td>M1</td>
<td>Coward</td>
<td>Morning</td>
</tr>
<tr>
<td>4.03</td>
<td>F2</td>
<td>Loser</td>
<td>Alright</td>
</tr>
<tr>
<td>4.04</td>
<td>M1</td>
<td>What a waste of space</td>
<td>They do it now</td>
</tr>
<tr>
<td>4.05</td>
<td>F2</td>
<td>Repulsive</td>
<td>Maybe</td>
</tr>
<tr>
<td>4.07</td>
<td>F1</td>
<td>Not good enough</td>
<td>The right thing</td>
</tr>
<tr>
<td>4.08</td>
<td>F2</td>
<td>No good</td>
<td>Same thing</td>
</tr>
<tr>
<td>4.19</td>
<td>F2</td>
<td>Look how ugly you are</td>
<td>Now you're going out of the door</td>
</tr>
<tr>
<td>4.21</td>
<td>F2</td>
<td>Everyone hates you</td>
<td>You remain silent</td>
</tr>
<tr>
<td>4.33</td>
<td>F1</td>
<td>Hey idiot</td>
<td>Hello</td>
</tr>
<tr>
<td>4.35</td>
<td>F1</td>
<td>Can't get rid of me</td>
<td>I send them</td>
</tr>
<tr>
<td>4.42</td>
<td>F2</td>
<td>Don't do that</td>
<td>Make me proud</td>
</tr>
<tr>
<td>4.48</td>
<td>M1</td>
<td>Can't get rid of me</td>
<td>I send them</td>
</tr>
<tr>
<td>4.55</td>
<td>F2</td>
<td>Wrong</td>
<td>Right</td>
</tr>
<tr>
<td>4.56</td>
<td>M1</td>
<td>Wrong</td>
<td>Right</td>
</tr>
<tr>
<td>4.58</td>
<td>F1</td>
<td>Mistake</td>
<td>Spring</td>
</tr>
<tr>
<td>4.59</td>
<td>F2</td>
<td>Stupid</td>
<td>Later</td>
</tr>
<tr>
<td>5</td>
<td>M2</td>
<td>No good</td>
<td>Same thing</td>
</tr>
<tr>
<td>5.01</td>
<td>M1</td>
<td>You're losing it</td>
<td>You're solid</td>
</tr>
<tr>
<td>Time (m:s)</td>
<td>Voice</td>
<td>NEG</td>
<td>NEU</td>
</tr>
<tr>
<td>-----------</td>
<td>-------</td>
<td>-------</td>
<td>----------</td>
</tr>
<tr>
<td>5.02</td>
<td>F2</td>
<td>Loser</td>
<td>Alright</td>
</tr>
<tr>
<td>5.03</td>
<td>F1</td>
<td>What a waste of space</td>
<td>They do it now</td>
</tr>
<tr>
<td>5.17</td>
<td>F1</td>
<td>Don't do that</td>
<td>Make me proud</td>
</tr>
<tr>
<td>5.18</td>
<td>F2</td>
<td>Hey idiot</td>
<td>Hello</td>
</tr>
<tr>
<td>5.3</td>
<td>F2</td>
<td>Stupid</td>
<td>Later</td>
</tr>
<tr>
<td>5.43</td>
<td>M2</td>
<td>Everyone hates you</td>
<td>You remain silent</td>
</tr>
<tr>
<td>5.48</td>
<td>M1</td>
<td>Worthless</td>
<td>Maybe</td>
</tr>
<tr>
<td>5.5</td>
<td>M2</td>
<td>They are laughing at you</td>
<td>You look like them</td>
</tr>
<tr>
<td>5.51</td>
<td>M1</td>
<td>Can't do anything right</td>
<td>Come and see us</td>
</tr>
<tr>
<td>5.52</td>
<td>F1</td>
<td>Repulsive</td>
<td>Alright</td>
</tr>
<tr>
<td>6.01</td>
<td>F1</td>
<td>Hey idiot</td>
<td>Hello</td>
</tr>
<tr>
<td>6.03</td>
<td>F1</td>
<td>Fraud</td>
<td>Spring</td>
</tr>
<tr>
<td>6.04</td>
<td>F2</td>
<td>Coward</td>
<td>Morning</td>
</tr>
<tr>
<td>6.06</td>
<td>F2</td>
<td>Look how ugly you are</td>
<td>Now you're going out of the door</td>
</tr>
<tr>
<td>6.08</td>
<td>M1</td>
<td>See how they look at you</td>
<td>You look like them</td>
</tr>
<tr>
<td>6.09</td>
<td>F1</td>
<td>Repulsive</td>
<td>Time to go to sleep</td>
</tr>
<tr>
<td>6.11</td>
<td>M1</td>
<td>They are laughing at you</td>
<td>You are laughing</td>
</tr>
<tr>
<td>6.12</td>
<td>F2</td>
<td>Repulsive</td>
<td>That's yours</td>
</tr>
<tr>
<td>6.13</td>
<td>M2</td>
<td>You're really a mess</td>
<td>You're solid</td>
</tr>
<tr>
<td>6.15</td>
<td>M2</td>
<td>You're losing it</td>
<td>You will return</td>
</tr>
<tr>
<td>6.2</td>
<td>M1</td>
<td>Can't do anything right</td>
<td>Today is the day</td>
</tr>
<tr>
<td>6.21</td>
<td>F1</td>
<td>Not good enough</td>
<td>The right thing</td>
</tr>
<tr>
<td>6.23</td>
<td>M1</td>
<td>Mistake</td>
<td>Spring</td>
</tr>
<tr>
<td>6.24</td>
<td>F2</td>
<td>Not good enough</td>
<td>The right thing</td>
</tr>
<tr>
<td>6.25</td>
<td>F1</td>
<td>Mistake</td>
<td>Spring</td>
</tr>
<tr>
<td>6.26</td>
<td>M1</td>
<td>Bad</td>
<td>Alright</td>
</tr>
<tr>
<td>6.27</td>
<td>M2</td>
<td>Loser</td>
<td>Later</td>
</tr>
<tr>
<td>6.38</td>
<td>M2</td>
<td>Go away</td>
<td>Be careful</td>
</tr>
<tr>
<td>6.39</td>
<td>M1</td>
<td>Stupid</td>
<td>Maybe</td>
</tr>
<tr>
<td>6.41</td>
<td>F2</td>
<td>Worthless</td>
<td>Morning</td>
</tr>
<tr>
<td>6.51</td>
<td>F2</td>
<td>They are laughing at you</td>
<td>It seems like a commercial</td>
</tr>
<tr>
<td>6.56</td>
<td>F1</td>
<td>Not good enough</td>
<td>The right thing</td>
</tr>
<tr>
<td>6.57</td>
<td>F2</td>
<td>Mistake</td>
<td>Spring</td>
</tr>
<tr>
<td>6.58</td>
<td>F1</td>
<td>You're losing it</td>
<td>Wait and see</td>
</tr>
<tr>
<td>6.59</td>
<td>M1</td>
<td>Can't do anything right</td>
<td>Time to go to sleep</td>
</tr>
<tr>
<td>7.01</td>
<td>M2</td>
<td>Don't do that</td>
<td>Make it really good</td>
</tr>
<tr>
<td>7.03</td>
<td>M1</td>
<td>Repulsive</td>
<td>Later</td>
</tr>
<tr>
<td>7.04</td>
<td>F2</td>
<td>They are laughing at you</td>
<td>You are laughing</td>
</tr>
</tbody>
</table>
Time (m:s) | Voice | NEG | NEU |
---|---|---|---|
7.05 | F2 | Stupid | Right |
7.06 | F1 | Can't do anything right | Today is the day |
7.08 | M1 | Hey idiot | Hello |
7.09 | M2 | They all know | They do it now |
7.1 | F2 | Mistake | Spring |
7.11 | F1 | Bad | Right |
7.12 | M1 | Crazy | Later |
7.14 | F2 | Don't do that | Make me proud |
7.15 | F1 | Crazy | Later |
7.16 | M2 | Should be ashamed | Come and see us |
7.17 | M1 | Go away | Be careful |
7.19 | F2 | What a waste of space | They do it now |
7.2 | F1 | Stupid | Right |
7.24 | M2 | Hey idiot | Hello |
7.25 | M1 | Stupid | Right |
7.26 | F1 | You're really a mess | You're solid |
7.27 | F2 | Everyone hates you | You remain silent |
7.39 | F2 | Can't do anything right | Today is the day |
7.45 | M1 | Hey idiot | Hello |
7.46 | F2 | Loser | Morning |
7.47 | M1 | Go away | Come and see us |
8.01 | F1 | Stupid | Later |
8.03 | M1 | Wrong | Right |
8.04 | F1 | Can't do anything right | Time to go to sleep |
8.05 | M2 | Loser | Spring |
8.06 | M2 | Loser | Spring |
8.07 | F1 | Hey idiot | Hello |
8.08 | F2 | Stupid | Alright |
8.11 | M2 | You're really a mess | You are coming |
8.25 | F2 | Not good enough | Time to go to sleep |
8.32 | F1 | What a waste of space | It’s just the way it is |
8.44 | F2 | Shame on you | You remain silent |
8.5 | M1 | Look how ugly you are | You look like them |
8.59 | M2 | Should be ashamed | Wait and see |
9.09 | M1 | Worthless | Morning |
9.15 | F2 | Stupid | Spring |
9.17 | F1 | Worthless | Morning |
9.18 | F2 | Wrong | Right |
9.19 | M1 | No good | Alright |
9.2 | M2 | Coward | Maybe |
9.21 | F1 | Mistake | Morning |
9.22 | M1 | Bad | Later |
9.23 | M1 | Stupid | Alright |
<table>
<thead>
<tr>
<th>Time (m:s)</th>
<th>Voice</th>
<th>NEG</th>
<th>NEU</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.23</td>
<td>F1</td>
<td>Stupid</td>
<td>Alright</td>
</tr>
<tr>
<td>9.25</td>
<td>M2</td>
<td>Not good enough</td>
<td>Make me proud</td>
</tr>
<tr>
<td>9.29</td>
<td>M1</td>
<td>Hey idiot</td>
<td>Hello</td>
</tr>
<tr>
<td>9.31</td>
<td>F2</td>
<td>Should be ashamed</td>
<td>Wait and see</td>
</tr>
<tr>
<td>9.38</td>
<td>M2</td>
<td>Loser</td>
<td>Later</td>
</tr>
<tr>
<td>9.39</td>
<td>M1</td>
<td>Stupid</td>
<td>Spring</td>
</tr>
<tr>
<td>9.48</td>
<td>F2</td>
<td>Can't do anything right</td>
<td>Time to go to sleep</td>
</tr>
<tr>
<td>9.49</td>
<td>M1</td>
<td>Give up</td>
<td>Come and see us</td>
</tr>
<tr>
<td>9.51</td>
<td>M2</td>
<td>Coward</td>
<td>Morning</td>
</tr>
<tr>
<td>9.52</td>
<td>F2</td>
<td>What a waste of space</td>
<td>Today is the day</td>
</tr>
</tbody>
</table>

F1 - Female Voice-Actor 1  
F2 - Female Voice-Actor 2  
M1 - Male Voice-Actor 1  
M2 - Male Voice-Actor 2
Appendix III – VAS Simulation Study

**VAS**

Participant ID: Date:
Time Point: ______ Exact Time:

Please put a mark on the line below to indicate you how feel *RIGHT NOW* from not at all stressed to very stressed.

<table>
<thead>
<tr>
<th>Not at all stressed</th>
<th>Very stressed</th>
</tr>
</thead>
</table>

Please put a mark on the line below to indicate you how feel *RIGHT NOW* from not at all anxious to very anxious.

<table>
<thead>
<tr>
<th>Very anxious</th>
<th>Not at all anxious</th>
</tr>
</thead>
</table>

Please put a mark on the line below to indicate you how feel *RIGHT NOW* from not at all angry to very angry.

<table>
<thead>
<tr>
<th>Not very angry</th>
<th>Very angry</th>
</tr>
</thead>
</table>

Please put a mark on the line below to indicate you how feel *RIGHT NOW* from not at all relaxed to very relaxed.

<table>
<thead>
<tr>
<th>Very relaxed</th>
<th>Not at all relaxed</th>
</tr>
</thead>
</table>

Please put a mark on the line below to indicate you how feel *RIGHT NOW* from not at all threatened to very threatened.

<table>
<thead>
<tr>
<th>Not at all threatened</th>
<th>Very threatened</th>
</tr>
</thead>
</table>

Please put a mark on the line below to indicate you how feel *RIGHT NOW* from not at all embarrassed to very embarrassed.

<table>
<thead>
<tr>
<th>Not at all embarrassed</th>
<th>Very embarrassed</th>
</tr>
</thead>
</table>

Please put a mark on the line below to indicate you how feel *RIGHT NOW* from expecting positive consequences to expecting negative consequences.

<table>
<thead>
<tr>
<th>Expecting positive consequences</th>
<th>Expecting negative consequences</th>
</tr>
</thead>
</table>

Please put a mark on the line below to indicate you how feel *RIGHT NOW* from socially judged to not socially judged at all.

<table>
<thead>
<tr>
<th>Socially judged</th>
<th>Not socially judged at all</th>
</tr>
</thead>
</table>
Appendix IV – Control Data

Participant ID: _____________ Date: _____________

Control data

Anthropometric:

Height: _____________ cm  Weight: _____________ kg

Concomitant medication:

Are you currently taking any medication? Y / N
If yes, please provide details (continue on reverse if required)

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose</th>
<th>Start date</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Do you suffer from any medical conditions? Y / N
If yes, please provide details:

________________________________________________________________________________________

________________________________________________________________________________________________________

________________________________________________________________________________________________________

Behavioural:

Time of last meal?: __________ Was it a (circle) - light breakfast / full breakfast / light meal / full meal

Description:

________________________________________________________________________________________

And in 4hrs prior to collection... please give description and approximate time consumed

Snacks? Y / N

________________________________________________________________________________________

Drinks? Y / N

________________________________________________________________________________________

Cigarettes? Y / N

________________________________________________________________________________________

If female: When was the first day of your last cycle? (dd/mm) -

________________________________________________________________________________________

When did you last perform strenuous exercise (e.g. weightlifting)?
Did you encounter any particularly stressful situations in the last 24 hours? Y / N  If yes, please provide details:

______________________________________________________________________________________________________________

Have you used any illicit substances in the last 72h? Y / N  If yes, please provide details:

______________________________________________________________________________________________________________
Appendix V – Cortisol Instructions

Measuring your biological levels of Stress:
A step by step guide for the saliva collection

Participant ID: ___________________ Date: _____________

For this test, we need you to take several saliva samples over the course of two consecutive days. Please carefully read the instructions on how to take the saliva samples. During the first day, you will take one sample IMMEDIATELY after waking up, before having brushed your teeth or having drunk or eaten anything. Then, you will take another sample at 3pm in the afternoon, and one at 8pm in the evening, again without having eaten or drunk in the preceding 30min. In the evening at 11pm you will take the pill of 1mg dexamethasone, and then repeat the same procedure for saliva sampling on the second day. Please store all tubes away from heat and direct sunlight and put them into a fridge as soon as possible. Please use this instruction sheet and fill out the boxes as you go along. If you have any questions about any of these instructions please call David Baumeister on 020 7848 5718 or 079 4479 8105. If agreed upon this before, you will receive a reminder phone call on the evening before the first day, and on the evening before the second day.

Day 1

Wake up (before 10 a.m.)
Immediately after waking up collect your saliva by chewing on the cotton wool pad for 2 minutes, then put it back in the tube with an orange dot marked 1. You should not eat or drink anything, or smoke or brush your teeth before.

Write here the EXACT TIME OF AWAKENING: ________________________

At 3 pm - collect your saliva using the tube with an orange dot marked 2. You should not eat or drink anything, or smoke or brush your teeth in the 30 minutes before 3pm.

• What time is it now?
______________________________

• What were you doing before giving the sample?
______________________________

• Did you accidentally have anything to eat or drink before taking the sample? If yes, please describe it here:
______________________________

• Did you have any difficult or tense situation, unpleasant thoughts or any kind of pain before taking this sample? If yes, please describe it here:
______________________________

______________________________
At 8 pm - collect your saliva using the tube with an orange dot marked 3. You should not eat or drink anything, or smoke or brush your teeth in the 30 minutes before 8pm.

- What time is it now?
- What were you doing before giving the sample?
- Did you accidentally have anything to eat or drink before taking the sample? If yes, please describe it here:
- Did you have any difficult or tense situation, unpleasant thoughts or any kind of pain before taking this sample? If yes, please describe it here:

Store the tubes away from the heat and direct sunlight and put them into the fridge as soon as possible.

Please note name and time of any medication taken today (including the contraceptive pill):

Instructions: Please swallow the pill of 1mg dexamethasone we gave you at 11:00pm (please note the exact time below). You do not need to fast before taking the pill, and you are allowed to drive after having taken it. You can also take any medication as usual, unless these are steroid creams or inhalers. You will not be able to eat or drink anything, or brush your teeth before your saliva sample is taken between the next morning. If you are unsure about any of the procedure, please let the research team know and they will give you a call to guide you through the procedure.

Time dexamethasone was taken: ______________________

Day 2 – following dexamethasone

Wake up (before 10 a.m.)
Immediately after waking up collect your saliva by chewing on the cotton wool pad for 2 minutes, then put it back in the tube with a blue dot marked 1. You should not eat or drink anything, or smoke or brush your teeth before.
Write here the EXACT TIME OF AWAKENING: ______________________
At 3 pm - collect your saliva using the tube with a blue dot marked 2. You should not eat or drink anything, or smoke or brush your teeth in the 30 minutes before 3pm.

- What time is it now?

- What were you doing before giving the sample?

- Did you accidentally have anything to eat or drink before taking the sample? If yes, please describe it here:

- Did you have any difficult or tense situation, unpleasant thoughts or any kind of pain before taking this sample? If yes, please describe it here:

At 8 pm - before dinner collect your saliva using the tube with a blue dot marked 3. You should not eat or drink anything, or smoke or brush your teeth in the 30 minutes before 8pm.

- What time is it now?

- What were you doing before giving the sample?

- Did you accidentally have anything to eat or drink before taking the sample? If yes, please describe it here:

- Did you have any difficult or tense situation, unpleasant thoughts or any kind of pain before taking this sample? If yes, please describe it here:

Store the tubes away from the heat and direct sunlight and put them into the fridge as soon as possible.

Please note name and time of any medication taken today (including the contraceptive pill):

If you are female: Please indicate the age of your first menstrual cycle:

And please indicate the date of the first day of your last menstrual cycle:
Collecting the saliva samples

1. Take the salivette marked with the appropriate number and carefully remove the lid (the part on the end with ridges on it).

2. Tip the cotton wool swab into the lid of the tube, then use this to place the swab in your mouth. **Do not touch the swab with your fingers.**

3. Gently chew the swab, repeatedly turning and moving it around in your mouth, for two minutes, so that it is saturated with saliva. This may seem longer than you expect, but the people in the laboratory need a lot of saliva for their analyses!

4. Take the swab out of your mouth with the help of the lid (so you are not touching it with your fingers) – it may be easier if you are looking in a mirror to do this. Tip the cotton bud back into the inner tube, again without touching the swab with your fingers.

5. Put the lid back on firmly.

6. Store the finished samples in the fridge.
## Appendix VI – VAS Clinical Study

### VAS

<table>
<thead>
<tr>
<th>Participant ID:</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Point:</td>
<td>Exact Time:</td>
</tr>
</tbody>
</table>

Please put a mark on the line below to indicate how you feel *RIGHT NOW* from not at all stressed to very stressed.

- Not at all stressed
- Very stressed

Please put a mark on the line below to indicate how you feel *RIGHT NOW* from not at all in pain to very much in pain.

- Not at all in pain
- Very much in pain

Please put a mark on the line below to indicate how you feel *RIGHT NOW* from not at all anxious to very anxious.

- Very anxious
- Not at all anxious

Please put a mark on the line below to indicate how you feel *RIGHT NOW* from not at all relaxed to very relaxed.

- Very relaxed
- Not at all relaxed

Please put a mark on the line below to indicate how you feel *RIGHT NOW* from not at all in control to not at all in control.

- Very in control
- Not at all in control

Please put a mark on the line below to indicate how you feel *RIGHT NOW* from not at all threatened to very threatened.

- Not at all threatened
- Very threatened

Please put a mark on the line below to indicate how you feel *RIGHT NOW* from not at all embarrassed to very embarrassed.

- Not at all embarrassed
- Very embarrassed
Please put a mark on the line below to indicate how you feel *RIGHT NOW* from expecting positive consequences to expecting negative consequences.

<table>
<thead>
<tr>
<th>Expecting positive consequences</th>
<th>Expecting negative consequences</th>
</tr>
</thead>
</table>

Please put a mark on the line below to indicate how you feel *RIGHT NOW* from socially judged to not socially judged at all.

<table>
<thead>
<tr>
<th>Socially judged</th>
<th>Not socially judged at all</th>
</tr>
</thead>
</table>
Participant Information Sheet

**Stress-reactivity in clinical and non-clinical voice hearers**

Ethics Reference Number: 15/LO/0880

The department of Psychology of the Institute of Psychiatry, Psychology & Neuroscience at King’s College London would like to invite you to take part in a research study. Before you decide to participate it is important for you to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully and ask us if there is anything that is not clear or if you would like more information.

**What is the purpose of the study?**

We are interested in speaking to people who report hearing voices, people or spirits talking to them that other people are not able to hear. We know that such experiences are more common than is often assumed, and are not necessarily related to mental illness. We are interested in gaining a fuller understanding of the different ways in which people respond and adapt to hearing voices or spirits. For some people these experiences have a positive impact and can be life-enriching. For others these experiences have a negative impact on their life and result in input from mental health services. This research will attempt to identify what distinguishes people whose voices are positive from those whose experiences become distressing. We are hoping that this understanding will help us in the future to find the best way to help people who have distressing voices.

Specifically, we are interested in understanding how the body’s stress system may be involved in the distress suffered by some voice-hearers. To do this we would like to compare the stress hormones, present in saliva, of three groups: individuals who hear
voices or spirits but are not troubled by them, individuals who find them distressing and have received some input from mental health services, and individuals who do not hear any voices and spirits.

**Why are we asking for your help?**

During the course of this study, which is conducted as part of a PhD project at King’s College London, approximately 70 people who are hearing voices or spirits will be asked to take part, as well as 35 people who do not hear voices or spirits. You have been invited to participate because you or an organisation you belong to has identified that you might be interested in helping with this research.

**Do you have to take a part?**

No, it is entirely up to you. We will describe the study to you and go through this information sheet, which you can keep. We will then ask you to sign a consent form to show that you have agreed to take part in the study, and will then ask a few questions to make sure you are able to take part.

You may choose to ask for independent information or advice about your rights as a research participant or about being involved in this particular research study by contacting the Research Governance Officer at King’s College London (please see below for contact details).

**What will happen if I start but don’t want to carry on with the study?**

Participants can withdraw from the study at any time without having to justify their decision. If you decide to withdraw from the study you can tell us whether you are happy for us to use the information obtained up to that point. If you are not, any information that you have given will be destroyed and you will not be contacted by us again.

**What will we ask of you if you take part in the study?**

The whole process will require an initial meeting to ensure that this research is right for you, and then two further separate appointments on two different days. Our initial chat should only take a few minutes and involves a brief consultation with a medical doctor to assess whether you can be included in the study. This is to make sure you are not currently taking any medication or suffer from medical conditions (such as diabetes, cardiovascular
disease and steroid allergies) that may make the study unsuitable for you, and, if you are female, this screening will include a pregnancy test. Then the day 1 appointment should take no more than 45 minutes, whereas the other appointments on day 2 and 3 should take no more than 1-1.5 hours, and will be carried out at the Institute of Psychiatry, Psychology & Neuroscience in Denmark Hill, London SE5.

For this project we will ask you to do several tasks that will allow us to measure your body’s stress system, which will help us understand how you respond to stress. First, we will ask you to take three saliva samples over the course of one day (when you first wake up, in the afternoon, and early evening). Then that evening you will take a pill called ‘Dexamethasone’ or ‘Dex’, which is a commonly used, very mild medication that interacts with your stress system. Then the next day you will take three more saliva samples, same as the first day.

This medication tells us how efficient your body is at recovering from stress and regulating itself. This is a procedure that has been carried out safely in many patients. The dose of medication is very small and will not affect your health, and it is very unlikely that it will change how you feel. At most, you may experience some headache or dizziness.

After you have completed this part of the procedure, we will invite you for your first appointment, where you will need to bring your saliva samples with you, and we will go through some questionnaires and interviews together (13 in total, each taking approximately 5-10 minutes). These questionnaires will ask about your current well-being, drug and alcohol use, mood and quality of life, as well as experience of hearing voices or spirits, and any previous stressful events in your life. This appointment should take no more than 1 hour. Some of the questionnaires will ask questions of a personal nature, but you don’t have to answer any question you feel uncomfortable with, and you can just move on to the following questions.

On the second appointment you will be asked to provide more saliva samples, before and after holding your hand in a container with very cold water for a short while. This will allow us to measure your body’s stress response to mild physical discomfort. During this
procedure, your facial expressions will be filmed for later analysis. You won’t be expected to have your hand in the cold water for very long, and in any case you will be free to remove your hand at any time if it becomes too uncomfortable. After you have finished we will then take several saliva samples over a 1 hour period, during which time you can just relax reading magazines. Overall the whole appointment should take no longer than 1.5 hours.

What are the possible disadvantages and risk of taking part?
Some of the questionnaires may cover issues that are sensitive, such as questions asking about previous stressful life events and drug/alcohol use. These questions are chosen to help us understand why some people become distressed by their voices and to find ways to help. You can choose not to answer any questions that you feel are too distressing or uncomfortable to answer, and just move on to the following questions, or you can stop the interview at any stage.

Both the ‘Dex’ test and the cold water task have been carried out in previous research studies without adverse events and have been approved by an independent NHS ethics committee. If ‘Dex’ medication is taken on a long-term basis (eg at high doses over a period of years) it can be associated with side-effects such as headache, dizziness, restlessness, irritability and anxiety, however a single low dose, as used in this study, typically do not produce any noticeable side-effects, and if any occurred they would be mild and transient. At the end of the study you will have a chance to tell us what your experience of participating in the research was like, and we will take this into consideration for this and future studies.

What are possible benefits of taking part?
There are no specific benefits to you in taking part in this study. However, you may find participating in our research interesting, and you will be remunerated for your time. The results of the study will hopefully help us to better understand how the body’s stress system is involved in why some people find voice-hearing distressing and others do not. It may also help to further develop interventions that specifically target these factors, such as mindfulness-based stress reduction.

Will I be compensated for my time?
We will reimburse any travel expenses that you incur and offer you £10 per appointment for your time. Reimbursement payment may need to be declared for tax or benefit purposes. If you think this may apply for you, please ask the researcher for more information, and look at the guidance linked below:

Will my taking part in the study be kept confidential?
All of the information you give for the study is treated confidentially. In the unlikely event that you were to tell us something that suggested that there would be a reason for us to be worried about harm to yourself, or to someone else we would have to breach this confidentiality. In these circumstances it would be important for us to share this information appropriately.

All the information and saliva samples you provide will be anonymised (ie your name will be removed) and you will not be identifiable in any research outcome. Only researchers belonging to the study team will be able to know which sample belongs to whom. The data will be handled and kept securely in line with the Data Protection Act and will be accessed only by the research team. Personal data will be stored securely at the Institute of Psychiatry, Psychology & Neuroscience for a maximum of 12 months after completion of the study and then destroyed. Data generated by the research will be destroyed after a maximum of 5 years after completion of the study. Should you wish to have your data destroyed after your participation, the deadline for any data withdrawal is 1 month following our meeting.

What will happen with the results of the research study?
We anticipate the study to be finished in early 2016, at the very latest in mid 2017. We will prepare a report of the results to share with colleagues in local, national and international meetings. The study will also be written up for publication in a scientific journal. We can send you a newspaper style article informing you about the results of the study, if you wish. Your questionnaires/interviews and samples will be coded and there will be no way of identifying who you are in any of the results or publications produced.

Complaints
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. If you have a concern about any aspect of this study, you can speak with the researcher in the first instance, or the researcher’s supervisor, Dr Emmanuelle Peters, who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the Director of Research Quality (see below).

**Harm**

**Compensation for harm arising from an accidental injury and occurring as a consequence of your participation in the study will be covered by King’s College London. If you are harmed and this is due to someone’s negligence then you may have grounds for legal action for compensation against King’s College London (with respect of any harm arising out of the participation in the research study).**

**Who has reviewed the study?**

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your safety, rights, well-being and dignity. This study has been approved by the London Dulwich Research Ethics Committee (reference 15/LO/0880). In addition this study has been reviewed and approved by the South London and Maudsley Foundation NHS Trust (SLaM) Risk Assessment Committee, and KCL Research & Development office. Thank you very much for your time and once again please ask for more information on the project if it is still unclear.

**Contact details for research team:**

David Baumeister  
PhD Student  
Institute of Psychiatry, Psychology & Neuroscience  
Tel: 0207 848 5718

Dr Emmanuelle Peters  
Reader in Clinical Psychology / Supervisor  
Institute of Psychiatry, psychology & Neuroscience
If you would like to speak to someone to get some independent advice about your rights as a research participant, you can contact the local R&D office:

**Research Governance Officer**  
King’s College London  
Box P005  
De Crespigny Park  
London, SE5 8AF  
Tel: 020 7848 0251

If you wish to make a complaint about the conduct of this study, you can do this through the Director of Research Quality:

**Dr Gill Dale**  
Director of Research Quality  
Joint R&D Office of South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, P005, Institute of Psychiatry (King’s College London), De Crespigny Park, London SE5 8AF  
020 7848 0675 / gill.dale@kcl.ac.uk

*We wish to thank you for taking the time to read this sheet and considering taking part in the research study.*

**Appendix VIII** – Flow Chart
First chat
- Chance for both of us to ask questions and decide together if this study is appropriate for you
- Fully explain what study consists of
- If you are eligible, and are happy to participate, then you sign the consent form

Day 1 Assessment
- We fill out questionnaires together
- We discuss the procedure for the saliva sampling

Saliva sampling
- We will ring/text you the evening before to remind you what to do
- First day: Do one sample when you wake up, one at 3pm and one at 10pm
- Take the pill (i.e. dexamethasone) at 11pm, repeat saliva sampling the next day exactly like on the first day

Day 2 Assessment
- At least 5 days after Day 1 Assessment
- You need to come to the meeting with your saliva samples
- Carry out cold pressor test (i.e. holding your hand in ice water)
- Collect saliva samples afterwards

Appendix IX – CAG Approval
Hi David

Following today’s Psychosis Research Committee meeting we are pleased to advise that your proposal for project title “Stress Reactivity in Clinical & Non-Clinical Voice Hearers” has been agreed in principle.

Please note the above Psychosis CAG reference number that has been allocated to the project which should be quoted in future correspondence with us.

Please note that you must not start your study until you have received formal written R&D approval from the SLaM/IoP R&D office.

In terms of the practical implementation of the project, your proposal has been forwarded to the following research leads who will be in touch with you to discuss the application in relation to staff capacity:

Acute Pathway:
Ijaz Rehman (Associate Clinical Director)

Complex Care Pathway:
Melinda Sweeting (Associate Clinical Director)

Recovery Pathway:
Suzanne Jolley (Consultant Clinical Psychologist for Lambeth Only)
Ros Ramsay (Associate Clinical Director)

Upon completion of the project could you kindly please forward a copy of your findings to us by email (CAGPsychosisRandD@slam.nhs.uk).

We wish you good luck with your project.

Kind regards
Sandra
Dear David

Re RAA2014-013 Stress-reactivity in clinical and non-clinical voice hearers—CI David Baumeister

I am pleased to advise that the risk assessment committee has now classified your study as within an acceptable level of risk and has approved the protocol. The risk assessment is now completed.

Adriana will now undertake the sponsorship review for your study. Could you please email Adriana the IRAS full project dataset and final protocol. If anything else is needed Adriana will be in contact with you.

Kind regards
Jenny

******************************************************************************
Jenny Liebscher
R&D Governance Manager
Joint R&D Office of South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology & Neuroscience (IoPPN)

PO05, Institute of Psychiatry, Psychology & Neuroscience (IoPPN)

020 7848 0251
jennifer.liebscher@kcl.ac.uk
Visit the R&D Office web pages at Research and Development Office

Read SLaM’s R&D Operational Capability Statement at R and D SLaM Operational Capability Statement 2014-2015
06 August 2015

Mr David Baumeister
PhD Student, Psychology
King’s College London
Room B4 04, Addiction Sciences Building
4 Windsor Walk, Denmark Hill
SE5 8BB

Dear Mr Baumeister

Study title: Stress-reactivity in clinical and non-clinical voice hearers

REC reference: 15/LO/0880
IRAS project ID: 149736

Thank you for your letter responding to the Committee’s request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Mrs Nischinth Cherodian, nrescommittee.london-dulwich@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion
The favourable opinion is subject to the following conditions being met prior to the start of the study.

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at [http://www.rdforum.nhs.uk](http://www.rdforum.nhs.uk).

Where a NHS organisation’s role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact [hra.studyregistration@nhs.net](mailto:hra.studyregistration@nhs.net). The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites
NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

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<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copies of advertisement materials for research participants [Recruitment poster]</td>
<td>1</td>
<td>27 April 2015</td>
</tr>
<tr>
<td>Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [KCL insurance]</td>
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<td>14 July 2014</td>
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<tr>
<td>Instructions for use of medical device [Instructions for meditation/relaxation]</td>
<td>1</td>
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<tr>
<td>Instructions for use of medical device [Instructions for Cold Pressor Test]</td>
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<td>Interview schedules or topic guides for participants [Flowchart clinical participants]</td>
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<td>Interview schedules or topic guides for participants [Flowchart non-clinical participants]</td>
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<td>Participant information sheet (PIS) [CVH]</td>
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Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback
The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

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<thead>
<tr>
<th>15/LO/0880</th>
<th>Please quote this number on all correspondence</th>
</tr>
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</table>

With the Committee’s best wishes for the success of this project.

Yours sincerely

Dr Michael Philpot
Chair

Email: nrescommittee.london-duwich@nhs.net

Enclosures:   “After ethical review – guidance for researchers”

Copy to:      Mr Keith Brennan
              Ms Jennifer Liebacher,
07 September 2015

Mr David Baumeister  
PhD Student, Psychology  
King’s College London  
Room B4.04, Addiction Sciences Building  
4 Windsor Walk, Denmark Hill  
SE5 8BB

Dear Mr Baumeister

Study title: Stress-reactivity in clinical and non-clinical voice hearers  
REC reference: 15/LO/0880  
Amendment number: AM01  
Amendment date: 14 August 2015  
IRAS project ID: 149736

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

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<td>Other [Recruitment Poster]</td>
<td>V2</td>
<td>14 August 2015</td>
</tr>
<tr>
<td>Participant information sheet (PIS) [Information sheet CVH]</td>
<td>Tracked v4</td>
<td>03 September 2015</td>
</tr>
<tr>
<td>Participant information sheet (PIS) [Information sheet HC]</td>
<td>Tracked v4</td>
<td>03 September 2015</td>
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<tr>
<td>Participant information sheet (PIS) [Information sheet HVH]</td>
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<td>03 September 2015</td>
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<tr>
<td>Research protocol or project proposal</td>
<td>V2</td>
<td>14 August 2015</td>
</tr>
</tbody>
</table>
Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members’ training days – see details at http://www.hra.nhs.uk/hra-training/

| 15/LO/0880: | Please quote this number on all correspondence |

Yours sincerely

Dr Michael Philpot
Chair

E-mail: nrescommittee.london-dulwich@nhs.net

Enclosures: List of names and professions of members who took part in the review

Copy to: Ms Jennifer Liebscher,
Mr Keith Brennan
## Attendance at Sub-Committee of the REC meeting on 07 September 2015

### Committee Members:

<table>
<thead>
<tr>
<th>Name</th>
<th>Profession</th>
<th>Present</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Martin Keech</td>
<td>Clinical Project Manager</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Dr Michael Philpot</td>
<td>Consultant Psychiatrist</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

### Also in attendance:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position (or reason for attending)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr Ali Hussain</td>
<td>REC Assistant</td>
</tr>
</tbody>
</table>
02 October 2015

Mr David Baumeister
PhD Student, Psychology
King's College London
Room B4.04, Addiction Sciences Building
4 Windsor Walk, Denmark Hill
SE5 8BB

Dear Mr Baumeister

Study title: Stress-reactivity in clinical and non-clinical voice hearers
REC reference: 15/LO/0880
Amendment number: Minor Amendment 30th September 2015
IRAS project ID: 149736

Thank you for your email of 30th September 2015 notifying the Committee of the above amendment. It is noted that the Five Facet Mindfulness Questionnaire (FFMQ), a fully validated questionnaire was submitted with the initial IRAS submission and explicitly mentioned in the approved protocol and A13 and A58 of the IRAS form. Due to a technical error with the system the FFMQ was not included in the original review.

The Committee does not consider this to be a "substantial amendment" as defined in the Standard Operating Procedures for Research Ethics Committees. The amendment does not therefore require an ethical opinion from the Committee and may be implemented immediately, provided that it does not affect the approval for the research given by the R&D office for the relevant NHS care organisation.

Documents received

The documents received were as follows:

Five Facet Mindfulness Questionnaire

Statement of compliance
The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

**15/LO/0880:** Please quote this number on all correspondence

Yours sincerely

[Signature]

Alison O'Kane
Acting REC Manager

Email: nrescommittee.london-dulwich@nhs.net

*Copy to:*  
Ms Jennifer Liebscher,  
Mr Keith Brennan
20 October 2015

Mr David Baumeister
PhD Student, Psychology
King’s College London
Room B4.04, Addiction Sciences Building
4 Windsor Walk, Denmark Hill
SE5 8BB

Dear Mr Baumeister

Study title: Stress-reactivity in clinical and non-clinical voice hearers
REC reference: 15/LO/0880
Amendment number: 3
Amendment date: 09 October 2015
IRAS project ID: 149736

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notice of Substantial Amendment (non-CTIMP)</td>
<td></td>
<td>09 October 2015</td>
</tr>
<tr>
<td>Participant consent form [CVH]</td>
<td>2</td>
<td>09 October 2015</td>
</tr>
</tbody>
</table>
Membership of the Committee

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R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

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15/LO/0880: Please quote this number on all correspondence

Yours sincerely

Dr Michael Philpot
Chair

E-mail: nrescommittee.london-dulwich@nhs.net

Enclosures: List of names and professions of members who took part in the review

Copy to: Ms Jennifer Liebscher,
Mr Keith Brennan

London - Dulwich Research Ethics Committee

Attendance at Sub-Committee of the REC meeting in correspondence
Committee Members:

<table>
<thead>
<tr>
<th>Name</th>
<th>Profession</th>
<th>Present</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Urmia Bapat</td>
<td>Pharmaceutical Physician</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Dr Michael Philpot</td>
<td>Consultant Psychiatrist</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>
### Appendix 1 - Research Interview and Distress Protocol

<table>
<thead>
<tr>
<th>Indications of Distress During Interview</th>
<th>Follow-up Questions</th>
<th>Participant Behaviour / Response</th>
<th>Acute Distress</th>
<th>Safety Concern</th>
<th>Imminent Danger</th>
</tr>
</thead>
</table>
| Indicate verbally that they are experiencing a high level of stress or emotional distress, AND/OR make facial expressions denoting emotional distress (eg anxiety/pain/anger etc) AND/OR exhibit behaviours suggestive that the interview is too stressful, such as crying, incoherent speech, etc. | 1. Stop the interview.  
2. Apologise, offer support and validation of distress. Allow participant time to regroup.  
3. Determine if participant is experiencing [acute emotional distress beyond what would be normally expected](https://example.com) in an interview about a sensitive topic. |                                | Y / N | Y / N | Y / N |
| Indicate that they are thinking of hurting themselves | 1. Stop the interview.  
2. Express concern, and conduct safety assessment in sensitive manner:  
   a) Do you intend to harm yourself?  
   b) How do you intend to harm yourself?  
   c) When do you intend to harm yourself?  
   e) Do you have the means to harm yourself?  
3. Determine whether participant is [imminent danger to self](https://example.com). |                                | Y / N | Y / N | Y / N |
1. If a participant’s distress reflects an emotional response **reflective of what would be expected in an interview** about a sensitive topic, offer support and extent the opportunity to: a) stop the interview; b) regroup; c) continue.

2. If a person’s distress reflects acute emotional distress or a safety concern **beyond what would be expected in an interview about a sensitive topic, but NOT imminent danger**, take the following actions:
   a. Encourage participant to contact his/her mental health provider or a significant other/friend/relative for follow-up and provide with follow-up contacts list.
   b. Provide the participant with emergency contacts and encourage the participant to call if they experience significant distress in the hours/days following the interview.
   c. Indicate that, with the participant’s permission, the researcher will contact them the next day to see if they are okay.
   d. Notify academic supervisors of the situation and recommendations given to participant.

3. If a participant’s distress reflects **imminent danger**, take the following actions:
   a. Contact local authorities unless arrangements can be made for the participant to be transported to the emergency room by researcher or a caregiver. Also contact the patient’s clinical team.
   b. Indicate that, with the participant’s permission, the researcher will contact him/her the next day to see if they are okay.
   c. Immediately notify academic supervisors of action taken and, if the adverse event is considered significant, inform REC and sponsor.

| Indicate that they are thinking of hurting others | 1. Stop the interview. |
| | 2. Express concern, conduct safety assessment in sensitive manner: |
| | a) Do you intend to harm someone else? Who? |
| | b) How do you intend to harm them? |
| | c) When do you intend to harm them? |
| | e) Do you have the means to harm them? |
| | 3. Determine whether participant is **imminent danger to others**. |

<table>
<thead>
<tr>
<th>Y / N</th>
<th>Y / N</th>
<th>Y / N</th>
</tr>
</thead>
</table>