The psychoneuroimmunology of music: modulation of psychological state, stress levels and immune response through participatory interventions

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Declaration

I, Daisy Fancourt, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Research into the health benefits of music has rapidly expanded over the last decade with recent studies showing early evidence of the ability of music to alter biomarkers of the neurochemical and neuroendocrine systems. However, it is not clear to what extent music can alter the response of the immune system. This thesis explores psychoneuroimmunological responses to music, in particular focusing on how participatory music interventions can modulate inflammatory responses. The biomarkers investigated include cortisol, a neuroendocrine stress marker, a range of pro- and anti-inflammatory cytokines within the immune system, the social bonding hormone oxytocin and the neuropeptide beta-endorphin.

Study 1 involved a six-week drumming intervention for mental health service users, and showed that drumming was associated with short-term increases in positive affect and cytokine activity and reductions in cortisol, and longitudinal improvements in depression, mental and social wellbeing, and reduced pro-inflammatory response. Study 2 replicated study 1 with a control group, showing comparable results at 6 weeks but also showing that if the intervention is extended to 10 weeks, there are also reductions in anxiety and all results are then maintained for 3 months following the end of the intervention. Study 3 aimed to explore the mechanisms of these effects in more detail. A randomised control trial comparing group drumming to three different control conditions showed that drumming, unlike the control conditions, leads to changes in a range of moods and emotions and the accompanying biological responses show signs of being associated with these emotions rather than with the physical parameters of group drumming. Study 4 extended the work of the previous mental health studies to explore how participatory music interventions can interact with the psychobiology of both mental health *and* physical health by studying patients affected by a chronic disease: cancer. A single session of group singing was found to be associated with reduced levels of cortisol, increased cytokine activity and, surprisingly, reduced levels of both beta-endorphin and oxytocin, again with associations between biological responses and emotions.

Given the prevalence of mental health conditions such as depression, either as a primary or secondary diagnosis, and evidence that such conditions are associated with heightened inflammation, participatory music interventions could offer novel opportunities for managing mental health and optimising immune function in patients.

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LIST OF ABBREVIATIONS

ANS autonomic nervous system

DF degrees of freedom

DHEA dehydroepiandrosterone

GC glucocorticoids

HPA hypothalamic-pituitary-adrenal

HR heart rate

IFN interferon

IL interleukin

MCP monocyte chemoattractant protein

OT oxytocin

SEM standard error of the mean

SD standard deviation

TGF transforming growth factor

TNF tumour necrosis factor

VAS visual analogue scale

1 SYSTEMATIC LITERATURE REVIEW

1.1 Introduction

1.1.1 The health benefits of music

Research into the health benefits of music has rapidly expanded over the last decade, driven both by a desire to understand more about the inner workings of music on the brain and body and in order to see how music can be better applied in community, educational and, in particular, healthcare settings (Stige, 2012). Breadth of study has ranged from the perception of folk songs inside the womb (Lemos, Tristao, Jesus, Melo, & Freire, 2011), to the performance of opera on concert platforms (Kenny, Davis, & Oates, 2004), and the use of pop music in operating theatres (Pluyter, Buzink, Rutkowski, & Jakimowicz, 2010).

The scientific study of music has gradually probed deeper into the mechanisms underlying the perception and processing of music, exploring the psychology of music (Hallam, Cross, & Thaut, 2008) and the cognitive neuroscience of music ('neuromusicology', (Peretz & Zatorre, 2003)). This depth of enquiry has included the neurological basis for music-induced emotions (Trainor & Schmidt, 2003); (Juslin, 2009), the neurobiology of certain aspects of music such as harmony (Tramo, Cariani, Delgutte, & Braida, 2003) and the neuroanatomy of music performance (Parsons, 2003).

In particular, neurological research has demonstrated the widespread effects of music on different parts of the brain. Acoustic information has been reported to be processed in the cochlea and then transformed in the auditory brainstem and the thalamus to filter out important auditory signals such as danger threats (Stefan Koelsch, 2010). In addition, the sensory cortex is activated in response to tactile feedback from playing an instrument, and the visual cortex in response to reading music (Levitin & Tirovolas, 2009). There has also been particular interest around rhythmic processing in the brain, with studies demonstrating activation of the primary sensorimotor and cingulate areas, bilateral opercular premotor areas, ventral prefrontal cortex, anterior insula, putamen and thalamus (Thaut, 2003). From the

thalamus, there is evidence that messages are sent to the auditory cortex (where specific musical information such as timbre is analysed before information enters the auditory sensory memory), and to the amygdala and medial orbitofrontal cortex (both involved in the processing of and response to emotion) (Koelsch, 2010). Other regions of the brain involved in the emotional processing of music include the hippocampus, parahippocampal gyrus and temporal poles (Koelsch, Fritz, Cramon, Müller, & Friederici, 2006), highlighting the pervasive neural effects of music.

In addition to these neurological studies, recent research outputs have begun to indicate a growing interest in the biochemical effects of music. Chanda & Levitin (2013) presented an overview of the neurochemical effects of music. And Kreutz, Quiroga Murcia, & Bongard (2012) overviewed the psychoneuroendocrine effects of music in order to test the assumption that 'psychological processes associated with musical experiences lead to changes in the hormonal systems of brain and body' (Kreutz et al., 2012, p. 457); something they label as 'perhaps one of the most fascinating areas of future research'. However, neither of these studies was systematic, and due to the respective specialised focus (neurochemical and neuroendocrine responses), they only examined a small subset of the markers that have actually been tested in relation to music. In addition, neither study looked at parallel physiological or psychological results, despite acknowledging that these psychophysiological states might have a relevance to the biological findings. This led Kreutz et al. to conclude that 'much more research efforts should be undertaken to ascertain the emerging patterns of changes that were reported in the available literature' (Kreutz et al., 2012).

1.1.3 This PhD

This PhD aims to explore psychobiological responses to music interventions in more detail, in particular focusing on how participatory music interventions can modulate inflammatory response both across individual sessions and longitudinally. This will be achieved through a range of methods of data collection and analysis, including validated psychological scales,

multiplexed saliva analyses of hormones, immune biomarkers and neurotransmitters, and heart rate and blood pressure monitoring.

The first part of this PhD involved undertaking a systematic review of the psychoneuroimmunological effects of music in order to analyse what patterns have been noted and which areas of enquiry provide the most promising avenues for future exploration. The full systematic review (Fancourt, Ockelford, & Belai, 2014) is published separately, but results from this review are summarised below.

1.2 Methods

To assess the current state of research on the interactions between music, stress and immunology, systematic database searches were conducted of Cochrane, Web of Science, PubMed, PsychINFO, Science Direct and Sage Journals, as well as manual searches of personal libraries. (See fig. 1) These sources were chosen as they were felt to give a comprehensive overview of the subject area, including in their compass journals from the disciplines of psychology, immunology, music therapy, music psychology, neuroscience, medicine, life sciences, social sciences and nursing, amongst others. Searches were made using the keyword 'music' paired with other keywords pertaining to stress and immunology: 'stress', 'immune', 'psychoneuroimmunology', 'cortisol', 'cytokine(s)', 'lymphocyte(s)', 'immunoglobulin', 'serotonin' and 'interleukin(s)'. The search returned 1938 articles, ranging from 1953-2013. After removing 568 duplicate studies, a total of 1371 studies remained.

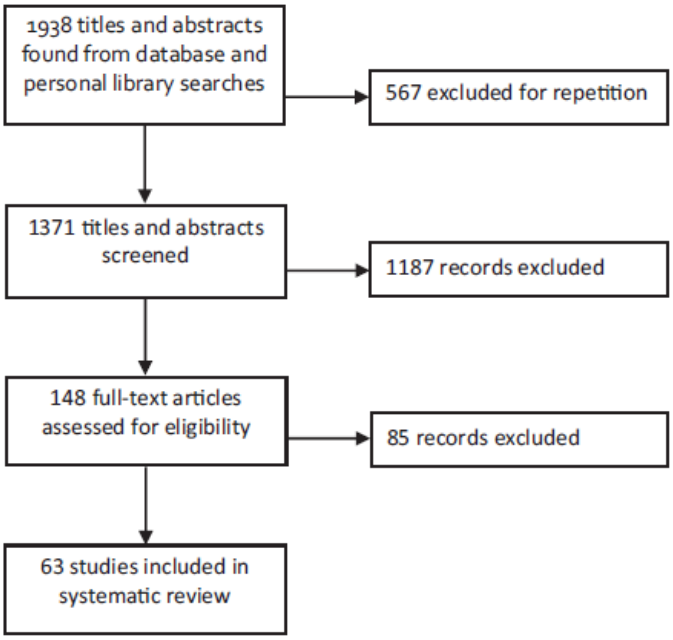


Fig 1. Collection of studies for inclusion in systematic review

Titles, abstracts and keywords were considered, and selection for inclusion in the review was made on the basis of three criteria. First, articles had to be a new study. Reviews were read, in particular for their references which brought to light some additional relevant studies to be considered, but were not included themselves. Secondly, studies pairing music simultaneously with other stimuli such as exercise, progressive relaxation or guided imagery were only included if they also contained a test incorporating just music on its own, as it was felt that the other stimuli could confuse results. Thirdly, studies had to be testing for potential positive effects of music, even if their results were negative or ambiguous. Studies were excluded if they deliberately tried to cause negative responses or distress through use of noise, loud volumes or heavy beats. Overall, this search was 'data-driven' in that a large number of keywords were included to identify a broad spectrum of studies, which were then scrutinised more closely against the inclusion criteria to assess their relevance to this review.

148 studies, ranging from 1983-2013, satisfied these criteria, so were then reviewed in full for key information including country of origin, study design, sample size, biomarkers monitored, genre of music used, mode of music delivery, and depth of immunological discussion. There was a great deal of variation in the methods applied in these studies. So in light of this, it was

decided that a meta-analysis aggregating the results of these studies was not possible, and instead a qualitative approach to assessing their findings was deemed to be more appropriate.

1.3 Results

1.3.1 Neuroendocrine responses

The review revealed a total of fifteen studies examining neuroendocrine response to music (see Table 1). The monoamine neurotransmitters adrenaline and noradrenaline were tested in twelve studies. Three studies involving relaxing recorded music reported a decrease in adrenaline and noradrenaline, and the same result was noted by (Okada et al., 2009) in response to music therapy, suggestive of a relaxation response. However, there were also several studies that did not report significant changes. Six of these studies involved participant selected music of various styles, which may have led to a confusion of relaxation vs stimulatory responses. Indeed, there have been a number of studies that have explored heart rate variability in response to music, many of which have shown different responses depending on arousal levels, suggesting a sympathetic nervous system involvement in music processing (Ellis & Thayer, 2010). Given that adrenaline and noradrenaline are also stimulated by sympathetic nervous system activity, it is plausible that they too alter in response to music dependent on arousal. Nevertheless, more work remains to be done to test this theory.

Table 1. Neuroendocrine responses to music

Study	Activity details	A	NA	Dopamine	β-end	MOR
Active participation						
(Okada et al., 2009)	Music therapy	↓	↓			
Recorded music – participant-selected (various styles)						
Wang et al. (2002)		-	-			
Lin et al. (2011)	(From a list)	-	-			
Chlan et al. (2007)	(From a choice of genres)	-	-			
(Migneault et al., 2004)	(From a choice of genres)	-	-			
Schneider et al. (2001)	(From choice of genres)	-	-			
(Mockel et al., 1995)	(From choice of genres)	↓ - [b]	↓ - [b]			
(Escher et al., 1993)	(With a music therapist)	-	-			
Recorded music – experimenter-selected (relaxing)						
(Conrad et al., 2007)		↓	-			
Brunges and Avigne (2003)		↓				
Stefano et al. (2004)						↑

McKinney et al. (1997)					↓	
Recorded music – experimenter-selected (stimulating)						
(Field et al., 1998)						
(Gerra et al., 1998)	Stimulating vs sedative	↑ - [a]	-		-	
Hirokawa and Ohira (2003)	Stimulating vs sedative	-	-	-		

Note: Arrows (↓ or ↑) indicate significantly higher or lower levels relative to both baseline and control conditions, unless otherwise specified. Dashes indicate no **significant** change. Blank fields indicate that the biomarker was not investigated. Abbreviations: A, Adrenaline; NA, Noradrenaline; β-end, beta-endorpin; MOR, μ-opiate receptor.

[a] The experimenters only found an increase with stimulating, not sedative music

[b] The experimenters found a decrease with sedative but no change for stimulating music

1.3.2 Endocrine responses

A total of thirty-two studies examined the effect of music on hormones (see Table 2). Twenty-nine included measurements of cortisol, of which eighteen studies reported reduced levels of cortisol whether through active participation or listening to recorded music. Interestingly, unlike adrenaline activity, decreases in cortisol were found across both stimulating and relaxing music. Cortisol/dehydroepiandrosterone (DHEA) ratio, which is also a marker of relaxation response, was also found to decrease when patients listened to relaxing recorded music, along with an increase in growth hormone (Conrad et al., 2007). However, when participants actively participated in performing music, there was an increase, suggesting that level of arousal is still important in endocrine response (Bittman et al., 2001).

Table 2. Endocrine responses to music

Study	Activity details	CORT	ACTH	CRH	DHEA	PRL	GH	OT	Test	CgA
Active participation										
Bittman et al. (2001)	Group drumming				↑[b]					
Lindblad et al. (2007)	Instrumental music lessons	↓								
Suzuki et al. (2005)	Music therapy									↓
Recorded music – participant-selected (various styles)										
Chlan et al. (2012)		-								
Lai and Li (2011)		↓								
(S. M. Wang et al., 2002)		-								
Milukkolasa et al. (1994)		↓								
Bartlett et al. (1993)		↓								
(Lin et al., 2011)	(From a list)	-								
(Schneider et al., 2001)	(From choice of genres)	^								
(Chlan et al., 2007)	(From a choice of genres)	-		- [a]						
(Mockel et al., 1995)	(From choice of genres)	↓[f]								
(Migneault et al., 2004)	(From a choice of genres)	-	-						↓↑ [c]	
Ventura et al. (2012)	(From choice of genres)	↓								

Leardi et al. (2007)	(From choice of genres vs new age)	↓ [g]								
(Escher et al., 1993)	(With a music therapist)	↑[e]	↑[e]							
Recorded music – experimenter-selected (relaxing)										
Nilsson et al. (2005)		↓								
(Uedo et al., 2004)		↑[e]								
Nilsson et al. (2009)		↓								
Nilsson (2009)								↑		
Khalfa et al. (2003)		↓								
Tabrizi et al. (2012)		^								
(Conrad et al., 2007)		-	-		↓	-	↑			
Knight and Rickard (2001)		↓								
Kar et al. (2012)		↓								
Urakawa and Yokoyama (2004)		-								
Fukui and Yamashita (2003)		↓								
Berbel et al. (2007)		↓								
Recorded music – experimenter-selected (stimulating)										
Koelsch et al. (2011)		↓	-							
(Field et al., 1998)		↓								
Yamamoto et al. (2007)	Stimulating vs sedative	↓ [h]								
(Gerra et al., 1998)	Stimulating vs sedative	↑↓ [d]	↑↓ [d]			-	↑↓ [d]			

Note: Arrows (↓ or ↑) indicate significantly higher or lower levels relative to both baseline and control conditions, unless otherwise specified. Arrows (v or ^) indicate that **without** music (i.e. in control groups), levels decreased or increased, but with music levels remained constant. Dashes indicate no **significant** change. Blank fields indicate that the biomarker was not investigated. Abbreviations: CORT, Cortisol; ACTH, Adrenocorticotropic Hormone; CRH, Corticotropin-releasing Hormone; DHEA, Dehydroepiandrosterone; PRL, Prolactin; GH, Growth Hormone, OT, Oxytocin; Test, Testosterone; CgA, Chromogranin A.

[a] The experimenters found an increase, but it was not significant

[b] The experimenters found an increase in the DHEA-cortisol ratio

[c] The experimenters found an increase for men and a decrease for women

[d] The experimenters found an increase with stimulating music and decrease with sedative music

[e] The experimenters found increase, but it was less in the music group than the control group

[f] The experimenters found a decrease for both stimulating and relating music

[g] Although cortisol levels decreased in both groups compared to controls, the experimenters found a significantly greater decrease in the group where patients selected their music from one of four styles compared to the group who listened to new age music

[h] The experimenters found a decrease only following low tempo music

1.3.3 Immune responses

Leukocytes

Six studies examined the effect of music on leukocyte subsets (see Table 3). Differing results were found depending on the nature of the intervention. For example, Bittman et al. (2001) found that natural killer cells increased when participants took part in stimulating group drumming sessions. In contrast, Leardi et al. (2007) found that for relaxing recorded music, natural killer cell levels decreased. And (Cai, Li, & Jiao, 2001) found that participatory music therapy sessions prevented levels of natural killer cells, along with CD4+ T cells, CD3, and the ratio of CD4 to CD8 cells from dropping. Given the differing levels of activity and arousal involved

in these three interventions, it is possible that levels of arousal in music interventions might also play a role in cellular activity. However, there were other variables between these studies such as degree of social interaction style of music and study design, so it is too early to be able to isolate these responsible variables properly.

Table 3. Immune responses to music: leukocytes

Study	Activity details	NK	CD4+T	CD8+T	CD4/CD8 ratio	CD16	CD 3	LYM	MT
Active participation									
Bittman et al. (2001)	Group drumming	↑							
(Koyama et al., 2009)	Group drumming		↑[a]					↑[a]	↑[a]
(Cai et al., 2001)	Music Therapy	v	v		v		v		
Live music – experimenter-selected (various styles)									
Staricoff et al. (2002)			-	↑					
Recorded music – participant-selected (various styles)									
Leardi et al. (2007)	(From choice of genres vs new age)	↓[c]							
Recorded music – experimenter-selected (stimulating)									
Hirokawa and Ohira (2003)	Stimulating vs sedative	-	↑ -[b]	-		-			

Note: Arrows (↓ or ↑) indicate significantly higher or lower levels relative to both baseline and control conditions, unless otherwise specified. Arrows (v or ^) indicate that **without** music (i.e. in control groups), levels decreased or increased, but with music levels remained constant. Dashes indicate no **significant** change. Blank fields indicate that the biomarker was not investigated. Abbreviations: NK, Natural Killer cell count; CD4+T, T helper cells; CD8+T, cytotoxic T cells; LYM, lymphocytes; MT, memory T cells.

[a] The experimenters found an increase only in older, not younger patients

[b] The experimenters found an increase only for stimulating music, not sedative

[c] Although cortisol levels decreased in both groups compared to controls, the experimenters found a significantly greater decrease in the group where patients selected their music from one of four styles compared to the group who listened to new age music

Cytokines

Eight studies reported the investigation of cytokines (see Table 4). Interleukin-6 showed the greatest levels of responsiveness, changing significantly in four out of the five studies in which it was tested. But other studies showed that cytokine activity might occur on a broader level than merely the alteration of single biomarkers. For example, Kimata (2003) found that relaxing music down-regulated levels of interleukins 4, 10 and 13 (Th2 type cytokines) and up-regulated levels of interferon-gamma and interleukin-12 (Th1 type cytokines) in patients undergoing an allergic response. These cytokine patterns were in direct contrast to the direction of up- and

down-regulation noted when these patients were made more stressed, indicating that music could lead to a relaxation response with biological correlates.

Table 4. Immune responses to music: cytokines

Study	Activity	IL-1	IL-1-beta	IL-2	IL-4	IL-6	IL-10	IL-12	IL-13	IL-γ	TNF-α	IFN-γ
Active participation												
Bittman et al. (2001)	Group drumming			-						-		
(Koyama et al., 2009)	Group drumming			-	-	↑↓ [d]	-					↑
(Okada et al., 2009)	Music Therapy					↓						
Recorded music – participant-selected (various styles)												
(Bartlett et al., 1993)		↑										
Recorded music – experimenter-selected (relaxing)												
Conrad et al. (2007)						↓						
(Stefano et al., 2004)			-			↓ - [b]	-					
(Kimata, 2003)					↓ [a]		↓ [a]	↑ [a]	↓ [a]			↑ [a]
Recorded music – experimenter-selected (stimulating)												
Lai et al. (2012b)	Stimuating vs sedative					c	c				c	

Note: Arrows (↓ or ↑) indicate significantly higher or lower levels relative to both baseline and control conditions, unless otherwise specified. Dashes indicate no **significant** change. Blank fields indicate that the biomarker was not investigated. Abbreviations: IL, interleukin; TNF-α, tumor necrosis factor alpha; IFN-γ, interferon gamma.

[a] The experimenters found results only in the presence of music by Mozart, not Beethoven

[b] The experimenters found a decrease in older adults, not younger adults

[c] The experimenters found tried to test 3 interleukins, but levels were all undetectable in the plasma due to breakdown

[d] The experimenters found an increase for older adults and a decrease for younger adults

Other immune responses

Thirteen studies examined the effect of music on immunoglobulins (see Table 5). Immunoglobulin A (IgA) was the most researched antibody (n=12), with eight studies reporting an increase in the level of IgA following a range of musical interventions. However, these results should perhaps be interpreted with caution, as there were discrepancies in IgA collection and analysis, with some studies actively stimulating saliva production which has been shown to also increase the amount of IgA secreted. In addition, a number of the studies simply involved IgA collection from saliva collected from the mouth, despite evidence to suggest that IgA proteases can also be collected this way and can break down IgA proteins during analysis. Furthermore, in a number of these studies, IgA was frequently taken as a single marker of the overall state of the secretory immune system, despite the fact that, especially when stimulated, only a small

percentage of IgA protein becomes antibody and plays a functional role in the immune system (Stone, Cox, Valdimarsdottir, & Neale, 1987).

Table 5. Immunological responses to music: antibodies and histamine

Study	Activity	IgA	IgE	Histamine
Active participation				
(Suzuki et al., 2005)	Music therapy	↑		
(Lane, 1994)	Music therapy	↑		
(Kuhn, 2002)	Singings vs listening to singing	↑[a]		
Recorded music – participant-selected (various styles)				
McCraty et al. (1996)	(From choice of genres)	↑ - [b]		
Recorded music – experimenter-selected (relaxing)				
Nilsson et al. (2005)		-		
Urakawa and Yokoyama (2004)		↑		
Knight and Rickard (2001)		↑		
(Kimata, 2003)			↓	-
(Kejr et al., 2010)		-		↓
Nomura et al. (2004)		↓		
Charnetski et al. (1998)		↑		
Recorded music – experimenter-selected (stimulating)				
Koelsch et al. (2011)		↑		
Hirokawa and Ohira (2003)	Stimulating vs sedative	-		

Note: Arrows (↓ or ↑) indicate significantly higher or lower levels relative to both baseline and control conditions, unless otherwise specified. Dashes indicate no **significant** change. Blank fields indicate that the biomarker was not investigated. Abbreviations: IgA, Immunoglobulin A; IgE, Immunoglobin E.

[a] The experimenters found the increase to be greater for active rather than passive involvement

[b] The experiments found an increase when the music was liked, but no change if patients disliked it

1.4 Discussion

In 2002, Nunez et al. (2002) reported that there was 'little information on the immunological response to … music'. This review demonstrated a clear increase in such literature over the past decade (40 studies 2003-2013, compared to 22 between 1993 and 2003, and only 1 study prior to this). The findings of these studies reveal changes across various biomarkers of immune response, including leukocytes, cytokines and immunoglobulins, as well as hormones and neurotransmitters associated with immune response. A few key conclusions can be drawn from this review:

1. There has been a general pattern of methodological weakness in studies conducted. The 63 studies included in the review were just a small proportion of over 1,000 studies claiming to

explore the effects of music on health; the majority were atheoretical qualitative papers, or papers claiming broad 'treatments' or even 'cures' to complex health conditions. Even controlled studies face challenges as the rhetoric around the 'healing' benefits of music is well established and can bias results. Amongst the 63 controlled psychobiology papers included in the review, the emphasis was on short (c. 1 hour) lab-based studies with healthy participants rather than any consideration of targeted interventions suitable to the demographics of the participants involved, repetitive exposure, or long-term effects. Research is needed that considers these issues in greater depth.

2. Many of the studies included in this review link the psychoneuroimmunological effects of music into the larger dialogue on music and stress. Indeed, music and stress have been the subject of several systematic reviews, (Austin, 2010; Avers, Mathur, & Kamat, 2007; Dileo, 2008). However, 'stress' is defined rather simplistically in music studies, with little consideration of the intensity or duration of the stressor. Furthermore, the consequent implications that a reduction of stress can impact on immune function are clearly not a part of the mainstream dialogue on music and stress, as none of these reviews even mentioned immune response. As a result, further research is needed to ascertain the extent of the relaxation effects of music on immune response.
3. The pervasive influence of music across so many components of the immune and endocrine system highlights that there is still much more to be explored as the vast majority of hormones, neurotransmitters and immune cells that are possibly involved in music-activated endocrine and immune pathways have yet to be examined. However, only five studies in the review considered the pathways activated in response to music interventions (Bittman et al., 2005; Conrad et al., 2007; Han et al., 2010; Koelsch et al., 2011; Tabrizi, Sahraei, Rad, Hajizadeh, & Lak, 2012). Other studies considered biomarkers in isolation, without referencing the mechanisms involved in their activation and release, nor their effect on other components of the immune system. Future studies could explore multiple biomarkers at once and identify in greater detail the pathways involved in response to music

in order to understand how interventions can be targeted more specifically to the needs of different patient groups.

4. The majority of studies in the review obtained blood samples for analysis, the exception being a few studies looking at cortisol or sIgA in isolation. Blood sampling is stressful for participants, which may compromise results when testing for the potential relaxation effects of a music intervention. Furthermore, papers did not consistently report the ways in which blood drawing and analysis took place, despite these procedures being known to have considerable effects on results (Zhou, Fragala, McElhaney, & Kuchel, 2010). Some studies even had difficulties detecting cytokines within blood (Lai, Li, & Lee, 2012).
5. The simple term 'music' has not been analysed in enough detail. Only four articles attempt to compare different modes of delivery, despite there being significantly increased relaxation found when participants sang rather than just listened to singing (Kreutz, Bongard, Rohrmann, Hodapp, & Grebe, 2004; Kuhn, 2002). Consequently, 'music' is in fact hiding a number of key variables any one of which could be responsible for psychoneuroimmunological changes, such as musical content, physical engagement, social involvement and personal response.

1.5 Theoretical model

In order to move forwards with the points noted from the systematic review, I proposed a new theoretical model for how music interacted with biological changes. In light of the relatively few articles that have explored precise pathways connecting our perception and reaction to music, it was decided to be premature to suggest a model that attempted to catalogue in detail the relevant psychological, neurological and immunological mechanisms involved. Instead, the results of this review suggested that three things would be of benefit from this model:

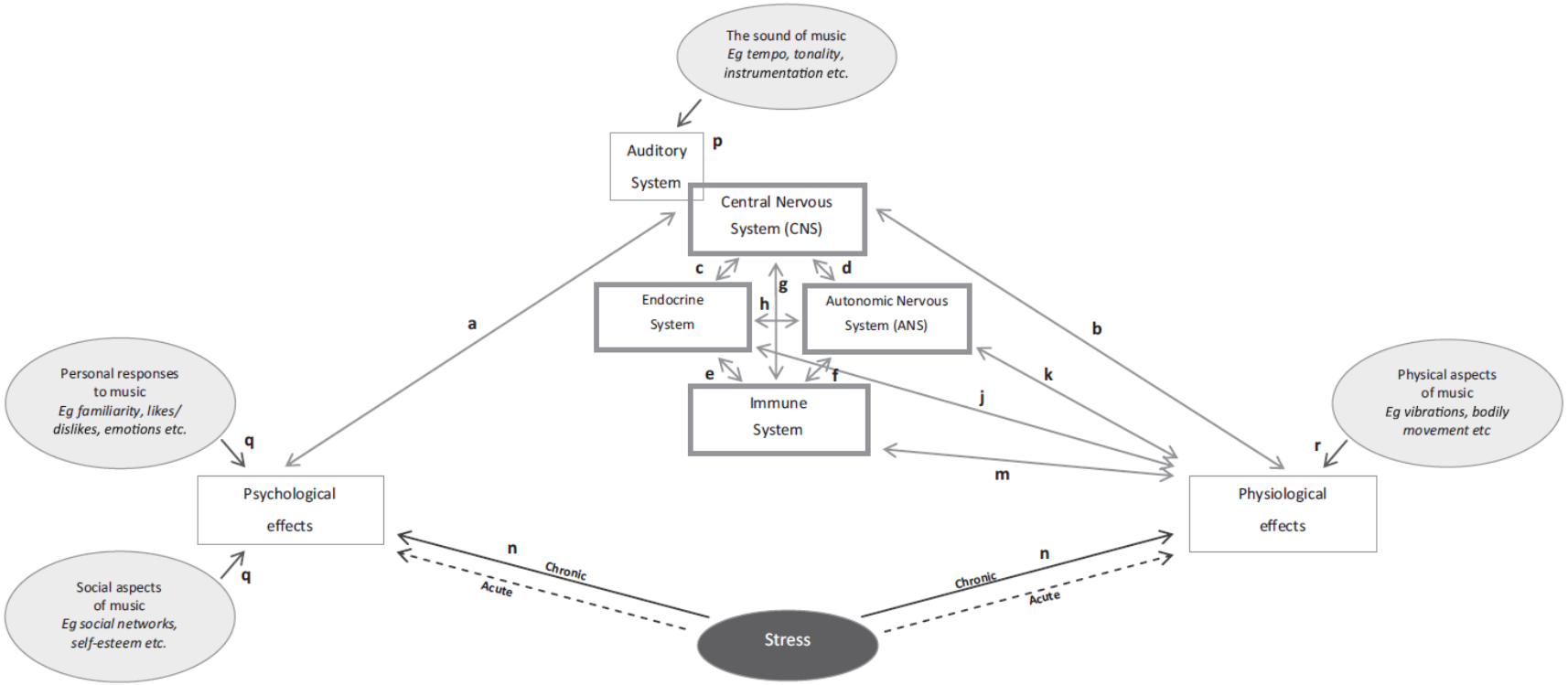
1. A way of giving more specific details of the variables involved in studies in terms of both the mode of music delivery and perception.

2. A way of giving more specific details of the types of stress being experienced by

participants involved in studies.

3. A broader view of how systems including the nervous, endocrine, and immune systems interact when a person is exposed to music, so that results from individual biomarkers can be situated within a wider context (see Figure 2).

Fig 2. A model of the system interactions involved in the psychoneuroimmunological response to music



Note: [a]Cacioppo and Decety (2009); [b]Andreassi (2013); [c] Asterita (1985); [d]Critchley (2005); [e]Besedovsky and Rey (1996); [f]Nance and Sanders (2007); [g]Sternberg (2006); [h]Ulrich-Lai and Herman (2009); [j]Turner (1994); [k]Jänig (1989); [m]Kelley (2004); [n]Lamb (1979); [p]Peretz and Zatorre (2003); [q]Hallam (2010); [r]Hodges (2008).

Building on previous research on psychobiological responses to stress, the model suggested two categories for the types of stress experienced by participants in studies; either naturally-occurring or induced for the purposes of the study (Pastorino and Doyle-Portillo, 2011; Lamb, 1997):

- Psychological stress (including social, personal or environmental changes, daily/microstressors and ambient stressors).
- Physiological stress (both within the body, such as viruses and bacteria, and outside the body, including exercise, injury, surgery, changes in outside temperature, exposure to chemicals etc.)

These two categories were then further subdivided into acute and chronic stress, following research demonstrating a difference in biological effect (Dhabhar & McEwen, 1997; Kudielka & Wüst, 2010). The model then proposed four different categories for how music can affect us (Peretz and Zatorre, 2003; Hallam, 2010; Hodges, 2008):

- The sound of music, as it is perceived by our auditory system. (Studies should specify key details that may be relevant, such as the tempo of piece of music, their tonality and their instrumentation.)
- Physical aspects of music (including the bodily actions required to produce the sound, as in singing or playing an instrument, as well as any strong musical vibrations that may have been perceived by participants).
- Social aspects of music (including whether participants socialised with others as part of the study, or reported an increase in confidence, pride or self-esteem).
- Personal response to music (including whether participants were familiar with the music; whether they liked or disliked it; or whether it elicited an emotional response).

The central part of the model linking together various neurological, psychological and physiological systems drew on research in the field of psychoneuroimmunology from the last decade (references provided in the figure). In line with findings of Solomon (1987), among others, these links were modeled as bidirectional. This central part aimed to demonstrate that psychological, neurological, endocrine and immune processes are intimately connected, such that if a marker within one of these systems is found to be affected, it likely has implications for other markers.

The overarching aim of this model was:

a. To provide a framework showing some of the broad interactions that have been discussed in the psychoneuroimmunology literature of the previous few decades to encourage the use of multiple biomarkers in future studies so that biological responses to music can be understood in a wider context, and facilitate discussions on the pathways being activated, hopefully increasing the literature in facets of music and psychoneuroimmunology that are currently understudied.
b. The encourage the definition of key variables involved in music interventions in order to begin to isolate which variables could be responsible for which biological changes.
c. To encourage the use of a range of psychological tests alongside the use of biomarkers to increase our understanding of the psychological and neurological pathways linking musical experiences to biological activity.

Within the context of this PhD, the model was used as an initial theoretical springboard. For studies throughout this thesis, detail is given as to how the interventions tested combine aural, social, physical and potentially personal features, and discussion sections focus on these issues. It also forms the focus of the third study in this PhD, guiding the study design and research questions.

1.6 Developments in biological analysis

Returning to the methodological issues noted in section 1.4, developments in the collection and analysis of biological samples may support future studies exploring the effects of music interventions. A recent paper by Bosch et al. (2014) discussed saliva as an alternative to blood analysis, outlined the mechanisms of transport and diffusion from blood to saliva and concluded on the benefits offered by saliva analysis for psychobiology research. Indeed, salivary cortisol and cytokines are already being used in studies across a range of other biological fields (Rhodus et al., 2005); (Pekiner, Gümrü, Demirel, & Özbayrak, 2009); (Dugué et al., 1996); (Thorman, Lundahl, Yucel-Lindberg, & Hylander, 2010); (Szczeklik, Owczarek, Pytko-Polończyk, Kęsek, & Mach, 2012) and new laboratory techniques for analysis are being developed (Blicharz et al., 2009; Slavish, Graham-Engeland, Smyth, & Engeland, 2015).

Previous studies have voiced a concern over a lack of correlation between salivary and serum or plasma cytokines, with only modest correlations found (Williamson, Munro, Pickler, Grap, & Elswick, 2012). However, (Byrne et al., 2013) tested 12 cytokines simultaneously in serum and saliva, finding high levels of detection in all 12 cytokines in saliva but only one cytokine in serum. Consequently, they argued that saliva analysis might yield some benefits, such as easier detection, than blood and correlations between saliva and blood should not necessarily be expected. There has also been a lack of consensus as to whether cytokines collected from saliva are indicative of local or systemic inflammation. However, several studies have demonstrated that neural pathways connect the inflammatory environment in the mouth directly to the central nervous system, suggesting that local inflammation may in fact be of relevance and interest in bio-behavioural research (Deinzer et al., 2005; Navarro, Iyomasa, Leite-Panissi, Almeida, & Branco, 2006).

As research around salivary analysis continues, it is timely to incorporate it into more studies, so this PhD uses the technique of multiplex saliva assays, while acknowledging that research into

salivary biomarkers is still in relatively early stages. From a methodological perspective, tests in this PhD will focus in particular on biomarkers whose activity in saliva has been most reliably determined. Cortisol is a well-established salivary biomarker widely used in biobehavioural research (Kirschbaum & Hellhammer, 1994; Kristenson, Garvin, & Lundberg, 2012), with particular value in measuring stress response. Several cytokines are also now becoming well recognised so are appropriate for inclusion within this PhD, most notably TNF-α and IL-6 (Slavish et al., 2015; Williamson et al., 2012). Both of these markers have also been identified as being of especial value in mental health research due to their involvement in inflammatory processes associate with conditions such as depression (Dowlati et al., 2010). However, there are other cytokines that are currently under-researched but have been identified as having promise (Slavish et al., 2015) such as IL-4 and IFN-ɣ. IFN-ɣ has also been found to be important in inflammatory processes associated with mental health conditions (Dowlati et al., 2010), and IL-4 provides an indication of anti-inflammatory response, which will help to establish the ratio of pro-inflammatory to anti-inflammatory activity. Consequently, these were selected as the core biomarkers for this PhD. Others are included, specific to each study, and the rationale for these is discussed accordingly. A list of all the biomarkers involved in this study and an overview of their roles is provided in Appendix 1.

2 PHD AIMS AND HYPOTHESES

2.1 PhD Aims

The aim of this PhD is to build on the studies analysed within the systematic review and explore the psychobiological effects of participatory music interventions both across individual sessions and longitudinally on different health populations. Data is being collected through two large studies: the Mental Health Project and Tenovus Cancer Choirs.

The Mental Health Project is an investigation of the effects of group drumming interventions on mental health service users. It is being undertaken in partnership with the Royal College of Music. It is split into 3 studies:

Study 1

Design: preliminary study

Participants: 31 adult mental health service users

Intervention: 6 weeks of 90-minute group-drumming workshops (Feb – March 2014)

Data collection: before and after the first and sixth session

Study 2

Design: controlled study

Participants: 30 adult mental health service users randomised into two experimental groups and 15 adult mental health service users as a control group

Intervention: 10 weeks of 90-minute group drumming workshops (October – December 2014) or control of no music intervention

Data collection: before the first, sixth and tenth session with three month follow up

Study 3

Design: within-subject randomised control trial

Participants: 100 adult mental health service users randomised into four groups

Intervention: four different drumming interventions (participating, watching a live performance, listening to a recorded performance and a control non-music activity) across four weeks (May – June 2014)

Data collection: before and after each session

These three studies were carried out as part of a Connected Communities Grant from the Art and Humanities Research Council, for which there were 10 research groups all exploring the impact of a different psychosocial intervention on mental health service users. These music studies were part of the Centre for Performance Science research group's project looking specifically at music interventions. I worked alongside Prof Aaron Williamon (the PI), Dr Rosie Perkins (the CI), and two other researchers: Sara Ascenso and Louise Atkins. I designed the studies along with Rosie and Aaron and then worked alongside Rosie, Sara and Louise in planning the interventions, selecting workshop leaders and recruiting participants. Rosie, Sara and Louise collected and analysed qualitative data for the project. I collected the quantitative psychological and biological data. The biological data were analysed by Aeirtec Ltd, where I assisted with the lab work. I performed the statistical analysis of all quantitative results and wrote up the findings. In addition, I was responsible for securing the funding necessary for the biological analyses and submitting the NHS ethical approval for the study.

Tenovus Cancer Choirs is an investigation into the effects of singing in choirs on cancer patients and carers. It is in partnership with the charity Tenovus Cancer Care's 'Sing With Us' choirs in Wales. It has one phase within this PhD and a second phase that will be carried out as a post-doctoral project:

Study 1

Design: preliminary study

Participants: 193 adult cancer patients and relatives split into five groups

Intervention: a single 70-minute choir session (June-July 2014)

Data collection: before and after the session

I sourced the funding for the project, designed the study and coordinated the ethical approval. Dr Ian Lewis and Rosie Dow from Tenovus Cancer Care carried out the data collection. The biological data were analysed by Aeirtec Ltd. I performed the statistical analysis of all psychological and biological results and wrote up the findings.

2.2 PhD Hypotheses

Objectives

Primary: To examine the effect of music interventions on both psychological and biological response

Secondary: To use multiplex testing to analyse a broad range of biomarkers and formulate hypotheses on the biological pathways being activated

To explore changes in psychological and biological response following a single music session

To explore the cumulative effect of music sessions over several weeks on psychobiological response

To examine the correlations between perceived alterations in mood with biomarkers

To ascertain how long-lasting effects of sessions can be following the end of an intervention

Hypotheses

H1: There will be an increase in positive psychological affect, decrease in stress response and increase in immune-enhancing activity evident immediately after a single session

H2: There will be a decrease in stress response and decrease in pro-inflammatory activity over multiple sessions.

H3: Decreases in levels of pro-inflammatory biomarkers will correlate with decreases in depressive symptoms.

H4: Psychological changes will be sustained for the three months following the end of a 10-week intervention

H5: Physically making music will lead to a greater modulation in emotion than watching or listening to music

H6: Short-term changes in emotions will correlate with biological activity

3 PART I: THE MENTAL HEALTH PROJECT

STUDY 1

3.1 Introduction

3.1.1 The biology of mental health

Worldwide, mental health conditions are the leading cause of disability-adjusted life years and, along with substance use disorders, are responsible for more of the global burden than HIV/AIDS, tuberculosis, diabetes or transport injuries. In the next 20 years, the global lost economic output as a result of mental health conditions will amount to $16 trillion (Whiteford et al., 2013).

Over the last fifty years, there has been growing evidence of biological pathways underpinning the pathophysiology of depression. Initial ideas centred round the 'monoamine hypothesis' (Schildkraut & Kety, 1967), which posited that deficiencies in synaptic concentrations of monoaminergic neurotransmitters, including noradrenaline and serotonin, were responsible for developments of depressive symptoms. However, studies in line with this theory found that the monoamine hypothesis did not provide a complete explanation for the biological underpinnings of depression, leading to a widened approach to immunological investigations into mental health.

In 1991, Smith formulated the 'macrophage theory of depression' (Smith, 1991), which hypothesised that pro-inflammatory cytokines produced by macrophages during the acute phase of immune response can act as neuromodulators that affect both the neurobiological and behavioural aspects of depression. This has since been labelled as the 'cytokine hypothesis of depression' or 'immune-cytokine model of depression' (ICMD) (Maes, 1999; Raison, Capuron, & Miller, 2006). Although disturbances of the cytokine network are not found in all patients, this model has nevertheless been found to be relevant for a range of mental health conditions, including bipolar disorder (Wieck et al., 2013) mood disorders (Dickerson & Kemeny, 2004) and

schizophrenia and psychosis (Di Nicola et al. 2013, Stojanovic et al. 2014). It is now widely accepted that mental health conditions involve a range of biomarkers, including a crucial interplay of monoamines, glucocorticoids and cytokines, all of which are described in more detail below.

3.1.2 Cytokines and mental health

Evolutionary evidence

The theory of inflammation and cytokines being involved in mental health has been supported not just by immunological studies, but also by evolutionary work. Infection has been the leading cause of mortality throughout human history (Finch, 2010). As a consequence of this, early humans, in particular Neanderthals, developed a strong inflammatory immune response to pathogens, with DNA clustering around the human major histocompatibility (MHC) locus. This inflammatory response may have protected early humans and continued to play an important role in survival today, but it carried with it a consequential vulnerability in the form of depressive symptoms. Despite the development since Paleolithic times of more immune regulatory pathways, in particular for repeat exposure to pathogens, these depressive symptoms are still a core feature of the immune system's response to threat. This theory of evolutionary inflammatory bias is supported by epidemiology studies showing that there is a high prevalence of comorbidity of depression with other chronic diseases (Evans et al., 2005).

The particular 'depressive symptoms' caused by an inflammatory bias are most commonly referred to as 'behavioural depression' or 'sickness behaviours': coordinated responses involving the reorganisation of behavioural priorities, first coined by Hart (1988). These responses typically happen in reaction to an infection and had the evolutionary purpose of both protecting the individual at risk, and also limiting their interaction with other members of the group to prevent the spread of illness (Anders, Tanaka, & Kinney, 2013). Preti has aligned these behaviours to the defence strategies of animals such as African naked mole rats and honey bees who self-sacrifice in order to avoid spreading infections to the rest of their kin (Preti, 2007).

However, in modern humans, heightened inflammation has been found to be a key mechanism that promotes diseases such as diabetes, cancer, myocardial infarction and cardiovascular disease (Maggio, Guralnik, Longo, & Ferrucci, 2006). Consequently, despite its evolutionary beneficial role, inflammation can exert a high toll on individuals.

Types of sickness behaviour can be split into somatic, cognitive and behavioural. Somatic symptoms include increased feelings of pain, appetite loss and suppressed locomotor activity. Cognitive include changes in mood, insomnia, fatigue, hypervigilance, anxiety and feelings of guilt. And behavioural changes are predominantly neurovegetative, including decreased motivation (Raison & Miller, 2013). These changes not only cause temporary psychological and physical changes but can work in a self-reinforcing manner. For example, avoidance of social activity can lead to feelings of social exclusion which can in turn undermine perception of belonging, control and self-esteem with detrimental consequences (Seidel et al., 2013).

Research data

A range of meta-analyses and epidemiological studies have shown associations between depression and increased peripheral inflammatory biomarkers (A. H. Miller, Maletic, & Raison, 2009). In particular, CRP and IL-6 have been highlighted as markers particularly associated with depression, with increasing evidence too for IFN-γ and TNFα (Dowlati et al., 2010). Although inflammation is not found in all patients with depression, but rather in somewhere between 30% and 50% of cases, it has been identified in mild cases as well as more severe cases. However, patients with depression exhibited decreases in cytokines levels proportionate to their rate of recovery when treated either with pharmacotherapy, psychotherapy or a combination of both (Dahl et al., 2014).

One less well established aspect pertains to the direction of causality: does depression predict inflammation or vice versa? A number of studies have shown that administration of pro-inflammatory cytokines to healthy subjects leads to sickness behaviour in the majority, with 50% of these going on to develop symptoms of major depression (Capuron et al., 2002). Significant research has also taken place in animal models, showing that administration of IL-1β and TNF-α led to suppressed locomotor activity, motivation, feeding and social exploration as well as weight loss, despair behaviour and a reduction in social interaction respectively (Iwata, Ota, & Duman, 2013; Slavich & Irwin, 2014). Conversely, studies in which anti-inflammatory treatments have been administered have shown reduced depressive symptoms (Köhler et al., 2014). However, other data have suggested that adverse events can be predictive of inflammation (Slopen, Kubzansky, McLaughlin, & Koenen, 2013). So it is still unclear, in a naturalistic environment, which one is the most frequent predictor.

3.1.2 Stress and mental health

In addition to monoamines and cytokines, glucocorticoids have also been found to play an important role in both the development and treatment of mental health. Psychological stress has been associated with increases in neuroendocrine stress response including cortisol (Segerstrom & Miller, 2004; Vedhara et al., 2003). However, acute increases in cortisol can lead to two responses: (1) negative feedback on the HPA axis, shutting off the release of neuroendocrine stress hormones (Pariante & Lightman, 2008); (2) reduced levels of pro-inflammatory cytokines and promotion of an anti-inflammatory response (Barnes, 1998; Elenkov, 2004, p. 1). However, chronic stress has been found to cause prolonged secretion of cortisol, which can lead to flattened diurnal cortisol curves, a decreased cellular responsiveness to cortisol (glucocorticoid resistance) and downregulation of cortisol receptors on leukocytes which can dysregulate the negative feedback loop and lead to excess inflammation (Bauer et al., 2000; Juruena, Cleare, Bauer, & Pariante, 2003; G. E. Miller, Cohen, & Kim, 2002). This has been found to be a bidirectional process between cortisol and inflammation as pro-inflammatory

cytokines can also reduce glucocorticoid receptor function (A. H. Miller & Raison, 2006). Cortisol has been found to be elevated in around 50% of patients with mental health disorders (Maes, Calabrese, & Meltzer, 1994), and has been linked with lower levels of serotonin (Cowen, 2002). However, normalisation of HPA axis activity has been linked with recovery with treatment, highlighting its importance in mental health research.

3.1.3 Interventions for mental health

Pharmacological models

The most well-established and common treatment for mental health conditions is pharmacotherapy. Three main categories of drugs are available: tricyclic and related antidepressants (TCAs), serotonin re-uptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs), although smaller categories also exist, as do herbal remedies such as St John's Wort. There is well-established evidence that pharmacological interventions can directly modulate the psychobiological problems underlying mental health conditions, but it is less established as to whether inflammatory responses are at the heart of this system. Some studies are showing evidence to support the inflammatory hypothesis, such as studies reporting reduced pro-inflammatory cytokine expression and increased Th2 expression in response to different classes of anti-depressants (Castanon, Leonard, Neveu, & Yirmiya, 2002), as well as studies demonstrating that anti-inflammatory medication can lead to anti-depressant effects (Muller, Marlowe, Bugumba, & Ellison, 2009). But more research remains to be done, particularly in relation to understanding the underlying mechanisms at play.

Despite major increases in antidepressant prescription, doubling in the US from 1995 to 2002 (LEON et al., 2006), there are still debates as to whether pharmacological interventions can provide a complete solution for patients, in particular when they are prescribed in isolation. Concerns pertain to a number of factors. For example, studies in depression have demonstrated that an average of only 50% of primary care patients will respond to anti-depressant medication, with a lag time of 8 weeks for changes to be noted (Arroll et al., 2005). Kraly has explored this

further, describing how behavioural changes can take longer to occur than the rebalancing of neurochemicals (Kraly, 2009). Furthermore, residual symptoms will persist in most patients, with only a third of those treated achieving remission after three months (Sobocki, Ekman, Ågren, Runeson, & Jönsson, 2006). There are also theories that over-treating mental health problems with drugs can medicalise the problem, leading patients to become more acutely aware of their emotional processes and believe their condition is out of their control, in a similar way that labelling conditions as diseases has been found to have a negative effect on self-management (C. L. Hoyt, Burnette, & Auster-Gussman, 2014). This can remove mental health conditions from the very socioeconomic environments in which they have developed, meaning that underlying socioeconomic issues and possible causes remain unsolved.

Other problems surrounding pharmacological approaches to mental health are around issues of non-adherence; estimated to be as high as 50% within just one month of starting (Butler, Chapman, Forman, & Beck, 2006); Lacro et al., 2002), and side effects. These range from weight gain, sexual dysfunction and cardiovascular disease risk, to agitation, anxiety and even increased suicide risk (Juurlink, Mamdani, Kopp, & Redelmeier, 2006; Roose, 2003).

Psychotherapeutic models

Another growing approach to the treatment of mental health conditions is psychotherapeutic interventions, in particular cognitive behavioural therapy (CBT). Like pharmacotherapeutic approaches, psychotherapeutics have been demonstrated to produce similar changes in brain neurochemistry (Kraly, 2009). Indeed, there is preliminary evidence that CBT can be more effective than anti-depressants for some adults with depression (Butler et al., 2006), with a lower relapse rate (29.5% for CBT and 60% for anti-depressants, (Gloaguen, Cottraux, Cucherat, & Blackburn, 1998). However, the field of psychotherapeutics is still under-researched. Meta-analyses comparing pharmacological and psychotherapeutic interventions have led to differing effect sizes (Bandelow, Seidler-Brandler, Becker, Wedekind, & Rüther, 2007; Khan, Faucett,

Lichtenberg, Kirsch, & Brown, 2012). So recommendations currently point to the benefits of combined pharmacological and psychotherapeutic interventions for mental health. This is reinforced by both a general wariness against prescribing psychotherapeutics on their own and a lack of special recommendations from institutions such as the National Institute for Clinical Excellence (NICE, 2009).

Psychosocial models

Alongside pharmacological and psychotherapeutic interventions, psychosocial therapies are increasingly appearing, often as an adjunct to conventional treatment as a way of increasing patients' involvement in their own mental health, encouraging health-promoting behaviours to enhance recovery, and reducing the load of symptoms. A recent systematic review found 69 psychological studies aimed at enhancing mental health and preventing depression or other mental disorders in those at risk or with sub-clinical symptoms (Forsman, Nordmyr, & Wahlbeck, 2011) with interventions including physical exercise, group support, reminiscence or social activities. Another review identified a further 11 studies involving tai chi, yoga and mindfulness that found reductions in inflammation or genome-wide transcriptional responses in carers or participants undergoing social stress (Slavich & Irwin, 2014). Their review argued for the potential of psychotherapeutic interventions in reducing inflammation.

3.1.6 Study introduction

One promising area within psychosocial interventions, but one yet to be fully researched as a therapeutic agent in mental health, is music. There have been several longitudinal studies exploring mental health and music making. For example, Erkkila et al. (2011) found significant improvements across 3 months of individualised music therapy with patients with depression. And (Talwar et al., 2006) found a trend towards improved symptom scores in schizophrenia patients in response to music therapy. However, these previous studies have generally taken place within specific institutions and used a music therapy model, led by a professional music therapist with specific psychological aims. A much less researched area is whether general music

making within community settings, not led by therapists, can still enhance the mental health and wellbeing of service users. This is an important topic to explore, as a growing number of organisations in the UK and abroad are developing community music interventions for mental health, including Youth Music UK and the Mental Health Foundation. Research into their efficacy is needed to ascertain whether they have a therapeutic effect and to support the design and implementation of future interventions.

One intervention of growing interest is group drumming, perhaps due to the inclusiveness of drumming circles, lack of fine motor skill requirements and strong steadying rhythms. There have been a number of studies to date involving group drumming. Winkelman (2003) identified drumming as a complementary tool for addiction treatments leading to reduction of alienation and self-centeredness through creating connectedness with self and others. Cammilieri (2002) explored drumming as a tool to enhance a sense of community in under-privileged neighbourhoods, while a recent study by Burnard & Dragovic (2014) highlighted the potential of drumming to enhance wellbeing with youth in educational contexts by a perception of empowerment and through the embodiment inherent to music learning. Within mental health settings, drumming has also been effective in the psychosocial rehabilitation of psychiatric in-patients (Tague, 2012) and in burn-out reduction for staff (Newman, Maggott, & Alexander, 2015). Furthermore, a study with alienated youth (Faulkner et al., 2012) highlighted the effects of drumming on social learning outcomes, including emotional control, improved relationships and increased self-esteem when combined with cognitive–behavioural therapy. The effect of drumming on social-wellbeing of at-risk youth was further reinforced by Wood et al. (2013). Two previous studies have also explored the biological effects of single sessions of group drumming on healthy participants, finding decreases in stress response and an increased Th1 cytokine profile following a single session (B. B. Bittman et al., 2001b; Koyama et al., 2009). However, there have been no studies exploring the combined psychobiological effects of group drumming

on mental health service users, despite previous studies providing a strong rationale for its potential as a psychosocial intervention for mental health.

Consequently, study 1 was designed as a preliminary study aiming to explore the effects of group drumming on mental health service users over a six week intervention. The study examined psychological, biological and cardiovascular responses across the six weeks as well as over individual sessions in order to assess whether drumming interventions can lead to reductions in stress and pro-inflammatory response. This is the first known study exploring the impact of a music intervention on the inflammatory response of mental health service users.

3.2 Methods

3.2.1 Design and participants

This was a preliminary uncontrolled study. Thirty-one participants took part (8 men and 23 women; mean age ± SEM: 52.8 ± 2.45 years) (see Figure 3). Participants were adults accessing mental health services with mild or moderate mental health conditions as categorised by the Hospital Anxiety and Depressions Scale (HADS). For this first phase, we applied a HADS cut off of 15 to focus the involvement on those with mild and moderate conditions. Participants were recruited from Chelsea and Westminster Hospital, Charing Cross Hospital and University College London Hospital; through psychologists working in NHS mental health services in North West London; or through professional mental health support organisations operating in London

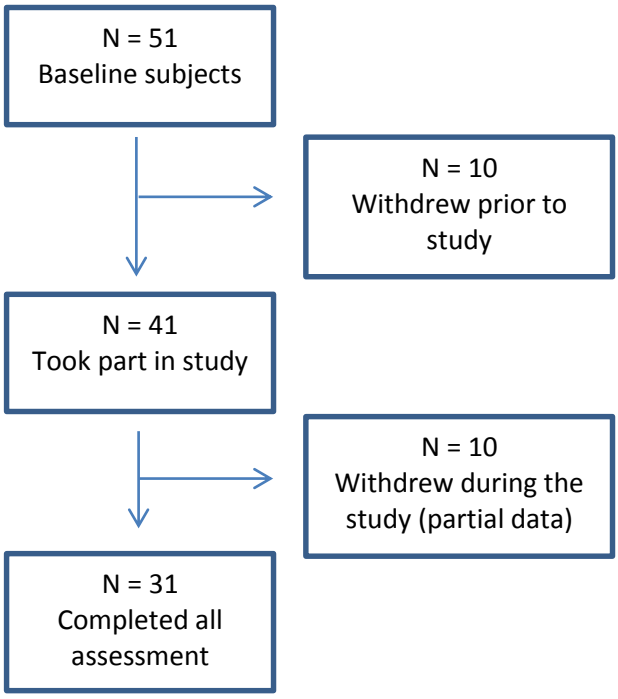


Fig 3. Recruitment of participants to study1

including MIND, Depression Alliance and Carers UK. A total of 65 participants were initially screened, but some participants were excluded if they had a dementia that prevented them from giving informed consent, or a severe hearing or physical impairment which would have prevented them from taking part in the drumming intervention. In order to minimise the effects of local inflammation, participants with gum disease were also excluded. Patients continued with their usual care during the intervention, but if there was a change to this usual care over the 6 weeks, such as commencing a new or different therapy, a change in their medication or a new diagnosis, they were retrospectively excluded from the analysis. The UK NHS National Research Ethics Service approved the project (reference 13/LO/1811) and all participants gave written informed consent prior to the study.

3.2.2 Procedure

Participants took part in weekly 90-minute group drumming sessions over a period of six weeks. They were split into two groups of 15 or 16 and sessions ran consecutively on weekday mornings in a hired community space in West London, led by a professional drummer and supported by three students from the Royal College of Music. Each participant was provided with a djembe drum and sat in a circle. The professional drummer taught the participants the basics of how to use the drum, led the participants in a series of 'call-and-response' exercises where participants copied whatever the leader did, and taught the participants rhythmic patterns that gradually built up over the six weeks into a larger drumming piece. Participants also had small sections of free improvisatory drumming creating musical accompaniment to different scenarios such as the sound of water. Talking took up an estimated 20% of the session time as the leader explained things to the participants, but the general teaching mechanism was by demonstration rather than verbal.

This study involved PhD hypotheses 1 and 2: we hypothesised that there would be an increase in positive psychological affect, decrease in stress response and increase in immune-enhancing activity evident immediately after a single session, and a decrease in stress response and decrease in pro-inflammatory activity over the entire six week intervention. Furthermore, we

predicted that biological response during the first session would be confounded by the anxiety of being in an unusual location with new people doing an unfamiliar activity, which could lead to less clear results, so we anticipated more reliable results from across the sixth session than the first. To test these hypotheses, in the week preceding and following the six week study, participants were asked to complete a pack of psychological scales. Immediately before and after the first and final sessions of the six-week intervention, participants gave a saliva sample. Furthermore, in order to examine psychological and physiological responses in more detail, immediately before and after the final session participants also filled in a set of visual analogue scales assessing mood states and had their blood pressure taken.

3.2.3 Psychological measures

Participants' socio-demographic and health characteristics were obtained by means of a set of self-administered questionnaires (see Appendix 2 for copies of all psychological measures). We assessed wellbeing using the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS); a questionnaire used extensively as a measure of positive mental health ranging from 14-70 with higher scores indicating better wellbeing (Tennant et al., 2007). We assessed anxiety and depression with the Hospital Anxiety and Depression Scale (HADS) (Bjelland, Dahl, Haug, & Neckelmann, 2002), ranging from 0-21 for each construct with higher scores indicating poorer mental health. We assessed social function with two scales, both of which were developed specifically for use in mental health: the Connor-Davidson Resilience Scale (CD-RISC), ranging from 0-100 with higher scores indicating stronger resilience; and the Secker scale for social inclusion, with higher scores indicating higher stress (Connor & Davidson, 2003); (Secker, Hacking, Kent, Shenton, & Spandler, 2009).

Visual analogue scales (VAS) were used to monitor stress, relaxation, happiness, tiredness and energy before and after an individual session. However, these were only included for session six. Initially, they had not formed part of the study design, but following on from the positive responses from participants over the first weeks, it seemed relevant to explore these in more detail. Participants placed a mark on a 100mm line labelled from 'not at all' to 'very' for each

construct and the distance was measured from left to right with higher values indicating greater intensity of the state being measured (Wewers & Lowe, 1990).

3.2.4 Biological measures

Given recent research demonstrating the variability in results when using stimulated saliva (Bosch, 2014), saliva was collected via a passive drool method facilitated by polypropylene straws into low-bind polypropylene 2mL cryovials (Eppendorf, UK). Participants were asked to refrain from eating or drinking for 20 minutes prior to providing a sample. All samples were given between 10am and 12noon to control for diurnal variation. Samples were stored at -20°C for a period of 2-8 weeks before transfer to -40°C for one month prior to analysis. Samples were vortexed and centrifuged before analysis. Supernatants were pipetted into 96 well filter plates (Millipore, UK) with microplex$_{TM}$ beads (Luminex Corp., USA) conjugated with antibodies to the analytes. All capture and detection antibodies and standards were purchased from Perotech, UK with the exception of TGF-β and TNF-α (R&D Systems, UK) and cortisol (antibodies from Abcam, UK, tracer from Randox, UK and standards from Sigma-Aldrich, UK). Following incubation for 24 hours, the beads were washed by filtration and then biotin-conjugated antibodies to the analytes were added to the beads for 4 hours. Following incubation with detection antibodies, the beads were washed and incubated with streptavidin-conjugated R-phycoerythrin for 45 minutes to provide a fluorescent detection signal. Following washing, the beads were analysed on a Luminex 100$_{TM}$ analyser.

Cytokines were chosen based on data suggesting which have been most reliably determined in saliva (see section 1.5.2) and can broadly be categorised as either pro-inflammatory (IL-2, IL-6, IFN-γ, TNF-α and MCP-1) or anti-inflammatory (IL-4, IL-10 and TGF-β), although some such as IL-6, IL-10 and TGF-β have been shown to have properties of both categories (Sanjabi, Zenewicz, Kamanaka, & Flavell, 2009; Scheller, Chalaris, Schmidt-Arras, & Rose-John, 2011) so these categories have to be interpreted with appropriate caution. More specifically, cortisol is a steroid hormone of the glucocorticoid class released in response to corticotropin-releasing hormone and adrenocorticotropin-releasing hormone in the brain. It has anti-inflammatory

properties (Cline & Melmon, 1966). IL-2 is involved in promoting the differentiation of immature T cells into regulatory T cells, memory T cells and effector T cells. It also plays an important role in regulating immune responses through negative feedback loops (Liao, Lin, & Leonard, 2011; Malek & Castro, 2010). IL-6 is secreted by leukocytes of both the innate and adaptive immune systems and has an immune-stimulating effect. However, it also inhibits certain pro-inflammatory cytokines such as TNF-α and IL-1. Importantly, IL-6 is capable of crossing the blood-brain barrier where it interacts with neurotransmitters such as serotonin (Scheller et al., 2011, p. 6; Stojanovic et al., 2014). IFN-ɣ is a pro-inflammatory cytokine expressed predominantly by natural killer cells and T lymphocytes. It is important for both innate and adaptive immune responses, such as activating macrophages (Schoenborn & Wilson, 2007). TNF-α is a pro-inflammatory cytokine. It plays an important role in the regulation of leukocytes as well as inducing apoptotic cell death and inflammation (Hickey et al., 1997). Dysregulation has been found in a range of conditions from depression to Alzheimer's to cancer (Dowlati et al., 2010; Swardfager et al., 2010). MCP-1 is a chemokine that recruits leukocytes including monocytes, dendritic cells and memory T cells to sites of inflammation (Carr et al., 1994). IL-4 is an anti-inflammatory cytokine involved in stimulating activated B-cell and T-cell proliferation, the differentiation of B cells into plasma cells and up-regulation of MHC class II production. IL-4 also decreases the production of macrophages and some pro-inflammatory cytokines such as IL-12 and IFN-γ (Choi & Reiser, 1998). IL-10 is an anti-inflammatory cytokine. It enhances B cell survival, proliferation and antibody production and can repress pro-inflammatory responses (Ouyang, Rutz, Crellin, Valdez, & Hymowitz, 2011). TGF-β plays a regulatory role. It promotes the induction of regulatory T cells in the thymus and in the periphery (Bird, 2010; Sanjabi et al., 2009). A full table of the role of these biomarkers is provided in Appendix 1. Lower and upper limits of quantification and limits of detection are given in Table 6. The inter-assay coefficient of variation range for all analytes was 1.8-5.37% and the intra-assay coefficient of variation range was 0.8-3.58%.

Table 6. Sensitivity and specificity data for cytokine analytes

Analyte	LOD (pg/ml)	LLOQ (pg/ml)	ULOQ (pg/ml)
IL-2	0.06	0.30	1000
IL-4	0.05	1.00	1000
IL-6	0.15	0.65	1000
IL-10	0.07	1.00	1000
IFN-γ	0.06	1.00	1000
TNF-α	0.02	0.10	1000
TGF-β	0.06	1.00	1000
MCP-1	0.06	1.00	1000

LOD: limit of detection; LLOQ: lower limit of quantification; ULOQ: upper limit of quantification

3.2.5 Cardiovascular measures

Blood pressure was assessed immediately before and after session 6 using Intellisense R2 wrist blood pressure monitors (Omron Healthcare Co., Ltd, Japan). As with VAS, blood pressure had not formed part of the initial study design, but was added just for the final session in order to explore participants' responses in more detail, in particular providing information on whether there were indications of physiological effect as well as psychological, neuroendocrine and immune effects. Readings were taken twice and averaged. If results from the two readings differed by more than 10%, readings were taken again.

3.2.6 Statistical analysis

Statistical analysis was performed using SPSS (Version 21.0, SPSS Inc., USA). We used repeated measures analyses of variances (ANOVAs) to test changes in subjective reports and immune measures across individual sessions and the whole intervention. Because of missing data at the different time points, we separately analysed measures before and after session 1, before and after session 6, and between the start of the study (beginning of session 1) and the end of the study (beginning of session 6). The distribution of all cytokines was positively skewed, so data were logarithmically transformed. If more than 50% of the values of a cytokine variable were not detectable, the variable was dichotomised as detectable or not detectable and analysed using McNemar's Test. This was applied to IL-10. Corrections for multiple comparisons were made using Bonferroni corrections. Three scenarios are presented. At the most conservative level, a total of 40 tests were undertaken, suggesting that an adjusted α should be 0.00125.

However, if a more lenient correction was applied and corrections were made according to the two research questions (longitudinal change = 14 tests and individual session change = 26 tests), an α of .0036 for the longitudinal change and .0019 for the individual session change should be applied. At a more lenient level still, if results are clustered according to type of data the following α values should be applied: longitudinal psychological data p<.01, short-term psychological data α<.01, short-term physiological data α <.017, longitudinal biological data α <.0056, short-term biological data α <.0028. We tested whether age and sex affected the observed differences in outcomes, but since they had no statistical effect we did not control for these variables in the final models.

3.3 Results

3.3.1 Demographic data

Table 7 presents demographic and psychological characteristics of the participants enrolled on the study. Most of the participants were white females. Participants showed baseline anxiety levels consistent with mild to moderate distress (mild, 8-10; moderate 11-14), mental wellbeing levels on the WEMWBS at the low end of average results (40-59) (Tennant et al., 2007) and social resilience scores considerably lower than the general population (80.7) and also lower than either psychiatric outpatients or those with generalised anxiety disorder (68 and 62.4 respectively) (Connor & Davidson, 2003).

Table 7. Demographics and psychological characteristics of participants in the intervention reported at baseline

	Total (N = 31)
Age, *M* ± SEM	52.8 ± 2.45
Gender, *n* (%)	
Female	23 (74.2)
Male	8 (25.8)
Ethnicity, *n* (%)	
White	22 (71.0)
Other	9 (29.0)
Employment, *n* (%)	
Employed / volunteer / student	12 (38.7)
Unemployed / retired / carer	19 (61.3)
Smokers, *n* (%)	2 (6.5)
Antidepressant medication, *n* (%)	7 (22.6)
Other medication, *n* (%)	4 (12.9)
Psychological Scales ± SD	
Hospital Anxiety Scale (HADSA)	9.33 ± 4.19
Hospital Depression Scale (HADSD)	6.27 ± 3.38
Connor-Davidson Social Resilience Scale (CD-RISC)	60.32 ± 16.47
Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)	37.45 ± 7.82
Secker Social Inclusion Scale (Secker)	44.55 ± 11.11

There were no significant differences in scores between any participants who dropped out and those who remained in the study.

3.3.2 Longitudinal results (across the six week intervention)

Psychological results

Across the entire intervention, a repeated measures ANOVA showed that depression scores using HADS significantly reduced from baseline ($F_{1,29}$=9.76, p=..004), wellbeing significantly increased ($F_{1,30}$=9.61, p=..004) and social resilience using CD-RISC also significantly increased ($F_{1,30}$=4.70, p=.038). These results are given in Table 8. Using the most lenient Bonferroni correction of α=.01, both HADSD and WEMWBS remain significant, but CD-RISC does not. Using the mid-level Bonferroni correction of α=.0036, both HADSD and WEMWBS just miss out on being significant. And nothing holds when applying the most rigorous Bonferroni correction.

Table 8. Psychological profile in participants before and after the 6 weeks

Scale	Baseline	After 6 weeks	F (n)	p
Mean ± SD				
HADSA	9.33 ± 4.19	8.27 ± 3.85	$2.80_{1,29}$[a]	.105
HADSD	6.27 ± 3.38	4.47 ± 3.08	$9.76_{1,29}$	**.004**
CD-RISC	60.32 ± 16.47	66.35 ± 17.35	$4.70_{1,30}$	**.038**
Secker	37.45 ± 7.82	38.35 ± 7.39	$0.74_{1,30}$	.396
WEMWBS	44.55 ± 11.11	49.71 ± 9.03	$9.61_{1,30}$	**.004**

[a] Number lower due to missing data

Biological results

Across the entire intervention, a repeated measures ANOVA found that four cytokines significantly decreased: IL-6 ($F_{1,14}$=9.94, p=.006), IFN-ɣ ($F_{1,15}$=9.13, p=..009), TNF-α ($F_{1,17}$=7.01, p=..017), and MCP-1 ($F_{1,17}$=10.06, p=..006). No significant differences were found for IL-2, IL-4, TNF-β or cortisol. For the dichotomised values of IL-10, no significant difference was found. These results are shown in Table 9. This demonstrates a lowering of pro-inflammatory cytokines, although there was no evidence of a decrease in stress response as shown through cortisol. Using the most lenient Bonferroni correction α=.0056, both IL6 and MCP1 just miss out on being significant, with nothing else holding. Using any stricter Bonferroni, none of the results hold.

Table 9. Saliva cytokine concentrations in participants at baseline and before session 6

Cytokine	Before session 1	Before session 6	F (n)	p
Mean ± SD (pg/ml)				
IL-2	1.86 ± 0.56	1.63 ± 0.79	$1.00_{1,13}$	.336
IL-4	0.78 ± 0.58	0.54 ± 0.44	$2.85_{1,15}$	.112
IL-6	0.44 ± 0.36	0.16 ± 0.17	$9.94_{1,14}$	**.006**
IFN-ɣ	2.00 ± 0.75	1.34 ± 0.65	$9.13_{1,15}$	**.009**
TNF-α	1.66 ± 0.38	1.47 ± 0.28	$7.01_{1,17}$	**.017**
MCP-1	2.78 ± 1.52	2.28 ± 1.49	$10.06_{1,17}$	**.006**
TNF-β	0.45 ± 0.32	0.40 ± 0.32	$0.285_{1,16}$	.601
Mean ± SD (ng/ml)				
Cortisol	1.81 ± 0.73	2.07 ± 0.75	$1.87_{1,17}$	.189
Dichotomised values (% detectable of total)				
IL-10	10/15 (67%)	6/15 (40%)		.104

3.3.3 Short-term results (within individual sessions)

Psychological results

Psychological data were collected before and after session 6 (the final session). From the beginning to the end of the session, a repeated measures ANOVA showed that stress and tiredness levels significantly decreased ($F_{1,32}$=11.95, p=.002 and $F_{1,32}$=14.92, p=.001) and happiness, relaxation and energy levels significantly increased ($F_{1,32}$=18.40, p=.001; $F_{1,32}$=23.28, p=.001; $F_{1,32}$=13.92, p=.001). These data are given in Table 10. Using the most lenient Bonferroni correction of α=.01, all results stay significant. Using the mid-level Bonferroni correction α=.0019, all results apart from stress remain significant. Using the most rigorous Bonferroni correction α=.00125, both happiness and relaxation remain significant.

Table 10. Mood states in participants before and after session 6

Scale	Baseline	After session 6	F (n)	p
Mean ± SD				
Stress	36.66 ± 25.40	20.86 ± 19.64	$11.95_{1,28}$	**.002**
Happiness	62.66 ± 22.53	78.90 ± 17.40	$18.40_{1,28}$	**<.001**
Relaxation	59.83 ± 25.76	81.07 ± 15.98	$23.28_{1,28}$	**<.001**
Tiredness	48.24 ± 26.18	32.52 ± 24.00	$14.92_{1,28}$	**.001**
Energy	56.90 ± 25.14	72.24 ± 17.60	$13.92_{1,28}$	**.001**

Biological results

Saliva samples were collected before and after session 1 and session 6. From the beginning to the end of session 1, the concentration of four cytokines significantly increased: IL-4, IFN-ɣ and MCP-1 ($F_{1,23}$=11.22, p=..003; $F_{1,23}$=8.43, p=.008; $F_{1,24}$=2.13, p=.157) and TGF-β ($F_{1,26}$=10.13, p=.004). No significant differences were found for IL-2, IL-6, TNF-α or cortisol, nor the dichotomised values of IL-10 (see Table 11). The pattern was different for session 6, where seven cytokines were significantly increased: IL-2 ($F_{1,13}$=9.53, p=.009), IL-4 ($F_{1,11}$=7.57, p=.019), IL-6 ($F_{1,12}$=12.34, p=.004), IFN-ɣ ($F_{1,12}$=24.12, p<.001), TNF-α ($F_{1,15}$=10.71, p=.005), MCP-1 ($F_{1,13}$=6.08, p=.028), and the dichotomised values of IL-10 (p=.024). Cortisol levels fell across session 6 ($F_{1,15}$=11.00, p=.004). Using any level of Bonferroni correction, only IFN-γ in week 6 maintained significance.

Table 11. Saliva cytokine levels in participants before and after sessions 1 and 6

Cytokine	Session 1		F (n)	p [c, e]	Session 6		F (n)	P[c]
	Before	After			Before	After		
Mean ± SD (pg/ml)								
IL-2	1.76 ± 0.64	1.93 ± 0.79	$2.11_{1,25}$	.159	1.67 ± 0.81	2.30 ± 0.78	$9.53_{1,13}$	**.009**
IL-4	0.62 ± 0.43	0.97 ± 0.68	$11.22_{1,23}$	**.003**	0.43 ± 0.19	1.00 ± 0.67	$7.57_{1,11}$	**.019**
IL-6	0.36 ± 0.31	0.41 ± 0.34	$0.63_{1,22}$	.435	0.15 ± 0.18	0.44 ± 0.31	$12.34_{1,12}$	**.004**
IFN-ɣ	1.63 ± 0.79	1.95 ± 0.89	$8.43_{1,23}$	**.008**	1.25 ± 0.68	2.22 ± 0.69	$24.12_{1,12}$	**<.001**
TNF-α	1.57 ± 0.36	1.69 ± 0.43	$3.31_{1,24}$	.080	1.43 ± 0.25	1.72 ± 0.39	$10.71_{1,15}$	**.005**
MCP-1	2.41 ± 1.28	2.70 ± 1.41	$2.13_{1,24}$	.157	2.03 ± 1.31	2.61 ± 1.19	$6.08_{1,13}$	**.028**
TGF-β	0.40 ± 0.27	0.60 ± 0.47	$10.13_{1,26}$	**.004**	0.36 ± 0.29	0.58 ± 0.35	$4.13_{1,14}$	.061
Mean ± SD (ng/ml)								
Cortisol	1.90 ± 0.56	1.89 ± 0.69	$0.00_{1,27}$	.952	2.13 ± 0.69	1.54 ± 1.08	11.00	**.004**
Dichotomised values[b] (% detectable of total)								
IL-10	17/25 (68%)	16/25 (64%)		.714	4/13 (31%)	9/13 (69%)		**.018**

As we initially hypothesised, both cytokine and cortisol responses were stronger in session 6 compared with session 1. In order to test this further, we also compared change scores calculated by subtracting the scores before a drumming session from scores after the same drumming session. This was only carried out for a subset of participants who had provided viable saliva samples above the level of detection at both time points in sessions 1 and 6 (see Table 12). We found that four biomarkers had significantly stronger alterations across session 6 compared with session 1: IL-2 ($F_{1,8}$=10.14, p=.013), IL-6 ($F_{1,8}$=8.16, p=.021), IFN-ɣ ($F_{1,8}$=31.86, p< 0.001) and cortisol ($F_{1,12}$=17.61, p=.001), with near significant results for the dichotomised values of IL-10 (p=.052).

Table 12. Saliva cytokine concentration change scores across sessions 1 and 6

Cytokine	**Change score**		**F (n)**	**p**
	Session 1	**Session 6**		
Mean ± SD (pg/ml)				
IL-2	-0.15 ± 0.38	0.70 ± 0.84	$10.14_{1,8}$	**.013**
IL-4	0.43 ± 0.61	0.77 ± 0.73	$2.24_{1,8}$	.173
IL-6	-0.52 ± 0.25	0.38 ± 0.30	$8.16_{1,8}$	**.021**
IFN-ɣ	0.25 ± 0.25	1.25 ± 0.47	$31.86_{1,8}$	**<.001**
TNF-α	0.05 ± 0.45	0.26 ± 0.29	$3.07_{1,11}$	.108
MCP-1	0.07 ± 1.13	0.75 ± 0.77	$2.66_{1,10}$	.134
TNF-β	0.03 ± 0.44	0.27 ± 0.46	$0.00_{1,10}$	.989
Mean ± SD (ng/ml)				
Cortisol	0.08 ± 0.63	-0.73 ± 0.79	$17.61_{1,12}$	**.001**
Dichotomised values (% detectable of total)				
IL-10	-1/10	4/10		.052

Cardiovascular results

We assessed cardiovascular activity before and after session 6. A repeated measures ANOVA showed that although blood pressure was not significantly reduced, there was a significant decrease in heart rate ($F_{1,32}$=15.35, p=.001), with an average change of 5.85 bpm. These data are given in Table 13. Using any level of Bonferroni correction, the change in pulse remained significant.

Table 13. Blood pressure in participants before and after session 6

Scale	Before session 6	After session 6	F (N)	P
Mean ± SD				
Systolic BP	118.12 ± 15.46	116.77 ± 15.66	$0.93_{1,32}$	.343
Diastolic BP	74.70 ± 11.50	73.07 ± 13.06	$0.86_{1,32}$	.361
Heart rate	77.93 ± 11.01	72.08 ± 13.05	$15.35_{1,32}$	**.001**

3.4 Discussion

The aim of this study was to explore whether a music intervention (group drumming) could produce improvements in mental health and inflammatory responses over several weeks, and as such whether music might be a promising psychosocial intervention for mental health service users.

We hypothesised that across an entire six-week intervention there would be a decrease in depressive symptoms, stress response and pro-inflammatory activity along with an increase in wellbeing. This was demonstrated by improvements in measures of depression, wellbeing and social resilience and decreases in pro-inflammatory cytokine response, but there was no evidence of a decreased neuroendocrine stress response as measured by cortisol. Furthermore, we hypothesised that across a single session within the larger intervention, there would be an increase in positive psychological affect, decrease in stress response and an increase in immune-enhancing activity as measured through increased cytokine activity evident immediately following the intervention. This was demonstrated by our results although, as predicted, this response was stronger across the sixth session than the first.

However, these results must all be interpreted in light of the Bonferroni corrections. Our results showed that, applying a lenient Bonferroni correction, some of the key results held, including the changes longitudinally in depression and wellbeing, all the short-term psychological changes, short-term changes in IFN-ɣ and short-term changes in pulse. Other results just missed maintaining significance, including longitudinal changes in IL6 and MCP1. However, applying the

strictest Bonferroni correction, only the short-term changes in happiness, relaxation, IFN-γ and pulse maintained. This could be indicative that the longitudinal results are not as robust statistically or should even be discounted. However, this was intended as an exploratory preliminary study with a small sample size, with the aim of assessing whether there were indications of change across different parameters. Consequently, the main aim of the study was to assess where change might be occuring in order to guide future studies, so corrections for multiple comparisons should be applied cautiously.

This study demonstrated for the first time that drumming interventions are associated with longitudinal changes in cytokine response. As Dahl et al. (2014) theorised, we found that that measurable improvements longitudinally in mental health occurred alongside reductions in pro-inflammatory response. Although not specifically analysed due to this being a preliminary study with low sample size, our data also suggest there was a rebalancing of pro- and anti-inflammatory response, with the significant decreases in pro-inflammatory markers. Overall, although there were non-significant decreases in anti-inflammatory markers, it may be that the ratio between pro- and anti-inflammatory biomarkers shifted across the six weeks. This will be interesting to explore in future studies.A secondary finding of this study is that a single session of drumming is associated with decreased cortisol levels and increase cytokine levels. This builds on the findings of previous drumming studies by Bittman et al. (2001) and Koyama et al. (2009) with healthy participants. Both studies looked at Th1 and Th2 activity rather than pro- and anti-inflammatory response and predicted that a single session of drumming would lead to decreased stress response and increased Th1 activity. However, although Bittman et al. found an increase in the DHEA-cortisol ratio, they found no changes in IL-2 or IFN-ɣ to support the Th1 shift (B. B. Bittman et al., 2001b). And Koyama et al. found increases in IL-6 and IFN-ɣ but no changes for IL-2, IL-4 or IL-10, giving an unclear picture as to Th1-Th2 balance (Koyama et al., 2009). By examining a broader range of cytokines alongside cortisol, this study was able to demonstrate clearly a reduction in stress response and an increase in cytokine activity in general,

suggesting that group drumming leads to an overall activation of the cytokine network rather than a shift towards either a Th1 or Th2 pathway. Furthermore, by examining multiple sessions, the study showed that stronger results are found in later sessions compared with the first sessions, suggesting either that initial nerves and anxiety can have a dampening effect on cytokine response in a first session or that the longitudinal effect of drumming over several weeks leads to more responsive immune activity to the intervention.

This study found data on perceived reductions in stress and increases in perceived relaxation noted from visual analogue scales (both $p<.002$) matched with decreases in cortisol and an immune-enhancing response, which could suggest that stress was a key mediator in the cytokine responses found. In support of this hypothesis, three systematic reviews have examined the stress-relieving properties of music and eighteen studies have demonstrated reductions in cortisol following listening to or taking part in music (Austin, 2010; Avers et al., 2007; Dileo, 2008; Fancourt et al., 2014). The repetitive, almost meditative, rhythms of group drumming, as well as ease of learning patterns through call and response, and the inclusiveness of drumming circles could be a therapeutic mechanism behind these effects, as could the physicality of emotion release through the act of drumming (Lazarus, 2006). Previous studies have demonstrated that stress is strongly linked with inflammatory pathways and depression, with dysregulation of stress and inflammation found in depressive patients, and evidence that depressive symptoms can enhance stress-induced inflammatory responses (Fagundes, Glaser, Hwang, Malarkey, & Kiecolt-Glaser, 2013; Rawdin et al., 2013). Iwata et al. (2013) have hypothesised that this is caused both through dysregulated activity in the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic-adrenal-medullary pathway, building on work of (Juruena et al., 2003) in showing the effects of dysregulated glucocorticoid response in patients with depression and affective disorders. Given the lack of changes in blood pressure noted in this study, it is possible that changes in the HPA axis are dominant,. However, this and theories of stress being the key mechanism behind effects here remain to be explored further in study 2.

This was an exploratory study and as such there are several limitations. Results were uncontrolled, so these data are preliminary and can only be interpreted with caution. This study also only examined drumming interventions over six weeks with a relatively small sample. Future studies are needed to assess the effects over longer timespans and with more participants. Furthermore, the intervention was analysed as a single entity. It would be instructive to examine which psychosocial or musical properties of group drumming are responsible for changes.

In conclusion, this preliminary study suggested that group drumming can lead to reductions in stress and immune-enhancement for mental health service users over individual sessions as well as reduce cytokine activity over a six-week span. Changes in biomarkers are supported by changes in psychological profiles of participants, demonstrating the potential of group drumming as an intervention for mental health. Further studies are needed to test fully the therapeutic potential of group drumming interventions and other music-based psychosocial interventions for mental health patients.

4 STUDY 2

4.1 Study introduction

In order to replicate and extend the findings from study 1, a second study was designed. This served several purposes, including to:

1. Confirm whether the psychological impact of group drumming could be replicated
2. Confirm whether psychological changes were any different to a control group who were not participating in regular musical activities
3. Confirm whether the reduction in pro-inflammatory response during drumming could be replicated
4. Assess whether a longer music intervention would produce stronger results
5. Assess whether results are maintained after the end of the intervention
6. Ascertain whether stress is a key mechanism in psychological changes

To test this, the protocol from the previous study was maintained, including the format of the drumming sessions themselves, but the number of weeks in the interventions extended, a control group recruited and additional measures added.

Building on our hypotheses in study 1 (PhD hypotheses 1 and 2), we hypothesised that group drumming would lead to reductions in reported anxiety, depression and stress alongside improvements in mental wellbeing and social resilience, with no systematic changes in the control group across the six weeks. Furthermore, we hypothesised that participants in the drumming group would show a reduction in pro-inflammatory immune response and a shift towards an anti-inflammatory immune profile alongside a reduction in the stress hormone cortisol. We also involved hypotheses 3 and 4: decreases in levels of pro-inflammatory biomarkers would correlate with decreases in depressive symptoms and psychological changes will be sustained for the three months following the end of the intervention.

4.2 Methods

4.2.1 Design and participants

This was a parallel group comparison of 10 weeks of drumming versus a control group who engaged in regular community-based (non-musical) social activities, with a 3-month follow-up of the drumming condition. Forty-five participants were allocated to two groups: 30 experimental and 15 comparison (see Figure 4). All participants were adults accessing mental health services as in study 1, but this time no upper limit was set on the severity of mental health condition as assessed using HADS. Recruitment was carried out as in study 1 with experimental participants recruited from West London near to the location of the intervention for ease of access. Control participants were recruited through the same channels but in South and North London, meaning that they met the same inclusion criteria but were not within the vicinity of the group drumming sessions to take part or were unavailable to participate due to other commitments. Although this was a non-randomised design and involved a control rather than a specific comparison group, all control participants also had to fulfil the criteria of taking part in regular group social activity (albeit not one involving music) in order to meet eligibility criteria. The aim of this was to recruit participants who were similarly interested in social engagement in order to align them more closely with the demographic of participants recruited to the experimental condition.

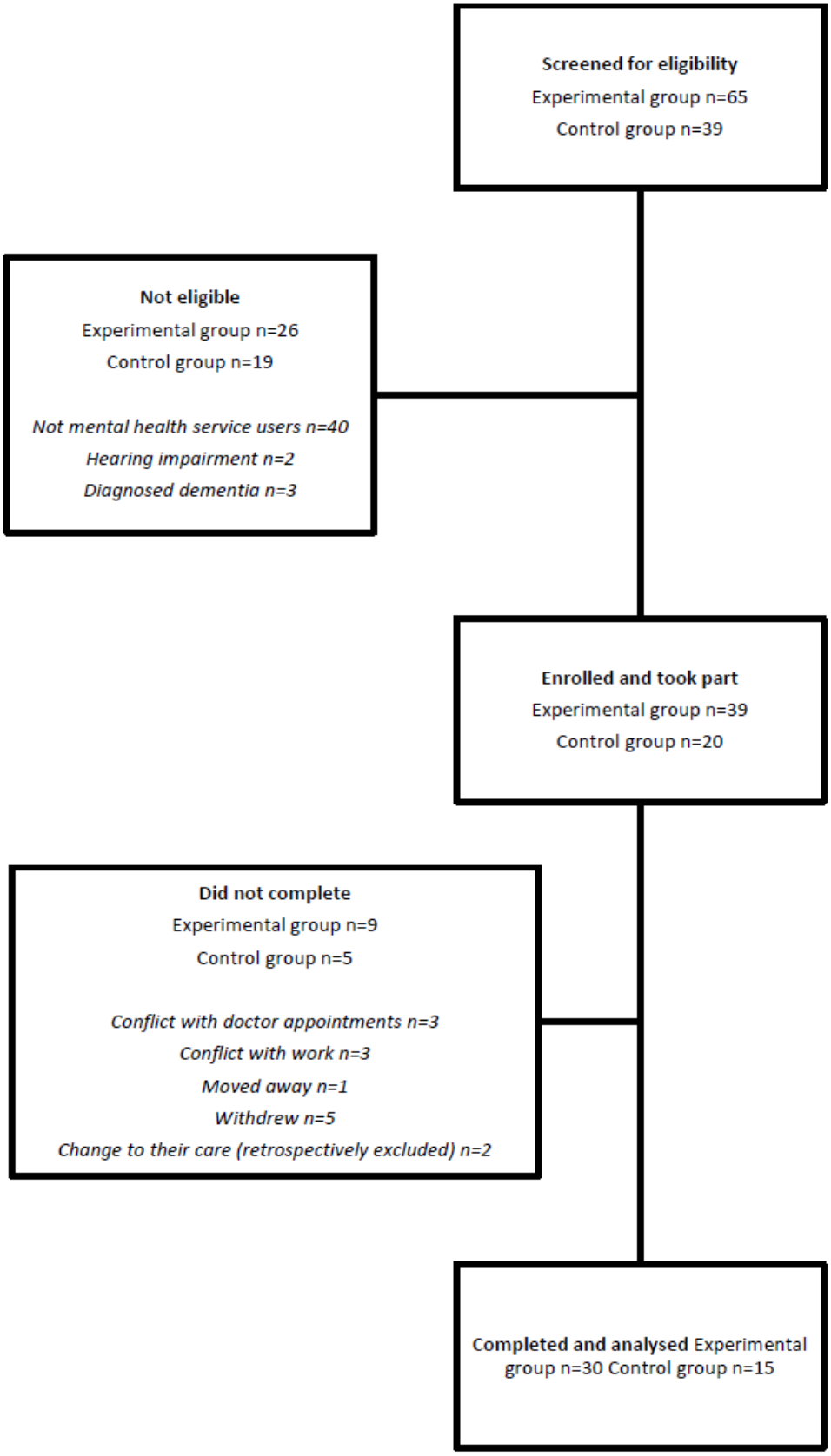


Fig 4. Recruitment of participants to study 2

4.2.2 Procedure

Experimental participants took part in weekly 90-minute group drumming sessions over a period of 10 weeks. Participants had to attend a minimum of 8 out of 10 sessions to be included in the analysis. Control participants did not take part in any group musical activities during the 10 weeks. However, to reduce the bias of having control subjects who were merely more socially isolated than the experimental group, all control subjects were already regular participants in community group social activities (e.g. quiz nights, women's institute meetings and book clubs) and continued with these activities for the duration of the study. No incentives were given to participants.

4.2.3 Psychological measures

Participants' socio-demographic and health characteristics were obtained by means of the same set of self-administered questionnaires as used in study 1. The scale was administered in the week preceding the first session in participants' own homes and again in the week following session 6 and session 10. However, as study 1 showed that drumming did not have any effect on the Secker social inclusion scale, this was not used. Furthermore, in order to test whether the effects of drumming were due to a change on how people perceive stress, the Perceived Stress Scale was added (Cohen, Kamarck, & Mermelstein, 1983). This scale ranges from 0-40 with higher scores indicating higher levels of perceived stress.

4.2.4 Biological measures

Saliva samples were taken before sessions 1, 6 and 10. Due to financial restraints, we did not assess change across sessions but just focused on the longitudinal impact, and we also only analysed biological samples from the drumming group. The samples were analysed for many of the same analytes as study 1: cortisol, IL-2, IL-4, IL-6, IFN-γ, TNF-α and MCP-1. However, due to the difficulty in detecting levels of IL-10, this was substituted for IL-17. An overview of the role of each biomarker can be found in Appendix 1.

4.2.6 Statistical analysis

Sample size was calculated using data from the previous six-week study with the primary endpoint of depression (HADSD) which showed an effect size of f=0.6. Using this effect size, an a priori sample size calculation using G*Power 3.1 for a between-factors ANOVAwith an alpha of 0.05, power of 0.9 and assuming two-sided tests and a correlation of 0.8 among repeated measures (2 groups, 3 timepoints) was made which showed that an overall total of 28 participants would be required (14 per group). For the control group, to allow for drop-outs of 30% (estimated based on the six-week study), 20 participants were targeted for recruitment. For the experimental group, because of the range of biological markers being tested, we decided to match sample size with our preliminary study (Fancourt et al., 2016), and so 39 participants were initially recruited. Recruitment was continued until these targets had been reached before being closed one week before the drumming started. Following drop-outs, 15 control and 30 drumming participants remained.

For psychological data, baseline scores between the two groups were compared using one-way analyses of variance (ANOVAs). For psychological data, we used 3 x 2 repeated measures ANOVAs to examine within-subject effects of time (baseline, week 6, and week 10), between-subject effects of condition (drumming vs control groups), and their interaction. We also used planned simple contrasts (week 1 vs week 10, week 6 vs week 10) to assess within-subject changes. Due to a difference in the baseline scores between the experimental and control groups in depression (HADSD), these data were also analyzed with a univariate analysis of covariance (ANCOVA) comparing the change scores between groups from weeks 1 to 6 and weeks 1 to 10, with the baseline values as a covariate in order to confirm whether change across time was significant when controlling for them.

For the follow-up psychological data, which were collected 3 months following the end of the intervention only for the experimental group, we used two repeated measures ANOVAs with within-subject effects of time: one ANOVA to assess whether final psychological levels were

significantly different from baseline (week 1 vs 3 months follow-up); and one ANOVA to assess whether final psychological levels were significantly different from the end of the intervention (week 10 vs 3 months follow-up).

For biological data, we again used repeated measures ANOVAs with time (baseline, week 6, and week 10) as the within-subject factor. The distribution of all cytokines was positively skewed, so data were logarithmically transformed prior to analysis. Given that cytokines can show rebound effects across time, we used planned polynomial contrasts to assess whether biomarkers showed linear or quadratic trends. We also employed a technique used in previous research exploring psychobiological responses in mental health (Song, Halbreich, Han, Leonard, & Luo, 2009), in which levels of TNF-α vs IL-4 were compared as markers of pro-inflammatory and anti-inflammatory profiles. For this, z scores for both biomarkers were created and comparisons were undertaken of their levels at baseline, week 6, and week 10 using t-tests.

Corrections for multiple comparisons were made using Bonferroni's correction, which showed that, at the most rigorous level accounting for all tests conducted, an α of .0038 would be needed to maintain significance. However, at a more lenient level, clustering psychological results and biological results, α values of .01 and .006 would be required respectively. As the design of this study was simpler than the previous study and just involved longitudinal measurements, a third level of leniency was not applied.

4.3 Results

4.3.1 Demographic data

Out of the initial 59 participants who enrolled on the study, 45 completed participation. Within these, experimental and control groups were well matched at baseline across all psychological measures except for depression, where the experimental group reported significantly higher levels (see Table 14). There were no significant differences between participants who completed and those who dropped out. Participants displayed moderate anxiety on the Hospital Anxiety and Depression Scale (HADSA: 10-15); mild depression in the experimental group on the Hospital

Anxiety and Depression Scale (HADSD: 8-10) (Zigmond & Snaith, 1983); social resilience scores below average adults (CDRISC: 80.7) and scores below those of generalized anxiety patients on the Connor-Davidson Social Resilience Scale (CDRISC: 62.4) (Connor & Davidson, 2003); mental wellbeing scores below the UK national average on the Warwick-Edinburgh Mental Wellbeing scale (WEMWBS: 51.6) (Mindell, 2012); and stress scores higher than average on the Perceived Stress Scale (PSS: 13), indicative of high stress (PSS: >20) (Cohen et al., 1983).

Table 14. Baseline demographics and psychological scales for experimental and control groups

	Drumming (n=30)	Control (n=15)	Difference
Female, *n* (%)	23 (77%)	14 (93%)	p=0.169[a]
Age, mean ± SD	55.07 ± 13.0	52.00 ± 14.7	χ^2_{44}=0.51, p=0.480
Ethnicity white, *n* (%)	21 (70%)	15 (100%)	χ^2_3=5.63, p=0.131
Status, *n* (%)			χ^2_3=7.19, p=0.066
Employed	4 (13%)	7 (47%)	
Retired	10 (33%)	4 (27%)	
Other	16 (53%)	4 (27%)	
Education			χ^2_3=0.47, p=0.925
No formal qualifications	4 (13%)	1 (7%)	
GCSE/A2	7 (23%)	4 (27%)	
Undergraduate qualification	13 (43%)	7 (47%)	
Postgraduate qualification	6 (20%)	3 (20%)	
Musical experience, *n* (%)			
Currently play an instrument	11 (37%)	11 (13%)	p=0.162[a]
Previously play an instrument	13 (43%)	8 (53%)	p=0.755[a]
Previous experience of drumming	0	0	p=1.00[a]
Regularly listen to drumming	0	3 (10%)	p=0.540[a]
Psychological scales, mean ± SEM			
HADSA	11.03 ± 0.83	9.93 ± 1.16	$F_{1,42}$= 0.591, p=0.446
HADSD	8.90 ± 0.79	4.27 ± 1.10	$F_{1,42}$=11.625, p=0.001
CDRISC	46.93 ± 3.47	57.85 ± 4.83	$F_{1,42}$= 3.385, p=0.073
WEMWBS	39.61 ± 1.91	44.67 ± 2.61	$F_{1,42}$= 0.355, p=0.555
PSS	23.17 ± 1.28	21.87 ± 1.78	$F_{1,40}$= 3.554, p=0.125

[a] Fisher's exact test

4.3.2 Psychological results

The analysis of anxiety ratings using a repeated measures ANOVA showed a significant condition by time interaction ($F_{2,84}$=3.63, p<0.05), with anxiety falling over the 10 weeks of drumming

while remaining unchanged in the control condition. Within-subject contrasts showed that this did not reach significance at 6 weeks but did reach significance by 10 weeks ($F_{1,42}$=5.357, p<0.05). The overall decrease in anxiety from baseline in the drumming group averaged 9% by week 6 and 20% by week 10 (see Table 15). Figure 5A shows the within-subject change from baseline at weeks 6 and 10 in both the drumming and control conditions.

The analysis of depression ratings showed a similar pattern, with a significant condition by time interaction ($F_{2,84}$=10.23, p<0.001). Depression fell over the 10 weeks of drumming while remaining unchanged in the control condition. Within-subject contrasts showed that this reached significance at 6 weeks ($F_{1,42}$=10.038, p<0.01) and was seen even more strongly by 10 weeks ($F_{1,42}$=17.048, p<0.001). The overall decrease in depression from baseline in the drumming group averaged 24% by week 6 and 38% by week 10. In the light of the baseline differences in depression ratings, we also analyzed change scores over time controlling for baseline levels; the difference between drumming and control conditions remained significant at week 10 ($F_{1,41}$=5.035, p<0.05). Figure 5B shows the within-subject change from baseline at weeks 6 and 10 in both the drumming and control conditions.

There was also a significant condition by time interaction for social resilience ($F_{2,84}$=5.13, p<0.01), with improvements in the drumming group but not the control group. Within-subject contrasts showed that this reached significance at 6 weeks ($F_{1,42}$=5.393, p<0.05) and was even stronger by 10 weeks ($F_{1,42}$=9.563, p<0.01). The overall improvement in social resilience averaged 16% by week 6 and 23% by week 10. Figure 5C shows the within-subject change from baseline at weeks 6 and 10 in both the drumming and control conditions.

In the analysis of the wellbeing scores, the condition by time interaction was nearly significant ($F_{2,82}$=2.91, p=0.06), with small improvements seen in the control group but larger changes in the drumming group. Within-subject contrasts showed that this was not significant at 6 weeks but did reach significance by 10 weeks ($F_{1,41}$=5.033, p<0.05). This improvement averaged 8% by

week 6 and 16% by week 10. Figure 5D shows the within-subject change from baseline at weeks 6 and 10 in both the drumming and control conditions.

The analysis of perceived stress showed a significant main effect of time ($F_{2,84}$=18.77, p<0.001) but no condition by time interaction (p=0.131); perceived stress fell over time in both groups. Figure 5E shows the within-subject change from baseline at weeks 6 and 10 in both the drumming and control conditions.

Using the strictest Bonferroni correction of α=.0038, only depression would have remained significant. However, using the more lenient version and just correcting the psychological tests together, both depression and social resilience would have remained significant.

Table 15. Psychological results in the drumming and control groups in weeks 1, 6 and 10

Scale	Baseline		Week 6		Week 10	
Mean ± SEM	**Drumming**	**Control**	**Drumming**	**Control**	**Drumming**	**Control**
HADSA	11.03 ± 0.83	9.93 ± 1.16	10.07 ± 0.77	9.20 ± 1.07	8.83 ± 0.70	9.60 ± 0.97
HADSD	8.90 ± 0.79	4.27 ± 1.10	6.76 ± 0.73	4.80 ± 1.02	5.48 ± 0.62	4.73 ± 0.87
CDRISC	46.93 ± 3.47	57.85 ± 4.83	54.62 ± 3.18	57.40 ± 4.42	57.52 ± 3.16	59.07 ± 4.39
WEMWBS	39.61 ± 1.91	44.67 ± 2.61	42.68 ± 1.94	46.47 ± 2.65	45.75 ± 1.80	47.00 ± 2.46
PSS	23.17 ± 1.28	21.87 ± 1.78	22.45 ± 1.34	18.07± 1.86	19.52 ± 1.12	16.00 ± 1.55

In order to evaluate whether the effect of group drumming on the psychological results was maintained after the intervention, the scales were administered with the drumming group at 3 months follow-up (during which time participants had not taken part in any drumming) and compared statistically with baseline levels. The observed changes were maintained, with significant differences at follow-up from baseline as shown in Figure 5 (HADSA: $F_{1,26}$=8.386, p<0.01; HADSD: $F_{1,26}$=16.703, p<0.0005; CDRISC: $F_{1,26}$=18.157, p<0.0005; WEMWBS: $F_{1,25}$=14.299, p<0.005). We also compared whether these follow-up levels had changed since the end of the intervention (week 10), finding no significant differences (HADSA: $F_{1,26}$=0.137, p=0.715; HADSD: $F_{1,26}$=0.273, p=0.606; CDRISC: $F_{1,26}$=0.795, p=0.381; WEMWBS: $F_{1,25}$=1.894, p=0.181). All results maintained significance with strict corrections.

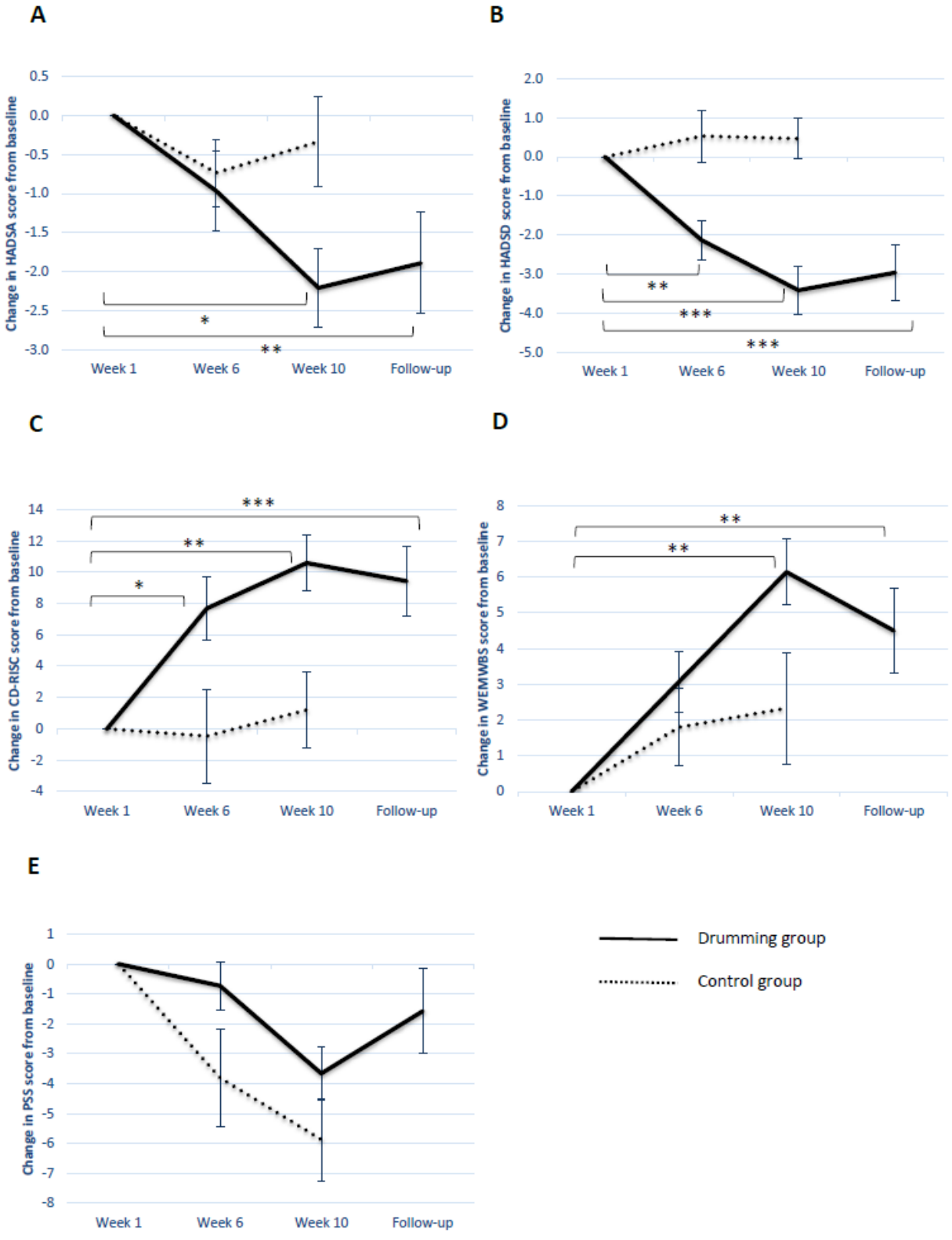


*Fig 5. Within-subject change from baseline (with standard error) at weeks 6 and 10 for drumming and control groups or (A) Anxiety (HADSA), (B) Depression (HADSD)(C) Social Resilience (CDRISC), (D) Mental Wellbeing (WEMWBS) (E) and Perceived Stress (PSS). * = p<.05, ** = p<.01, *** = p<.001.*

4.3.3 Biological results

In order to explore the mechanisms of change in the drumming group, saliva samples were obtained to assess if there were also changes in immune biomarkers.

Table 16. Saliva cortisol and cytokine concentrations in participants at baseline and before sessions 6 and 10

Biomarker	Week 1	Week 6	Week 10	F(n)	p
Mean (SEM) (ng/ml)					
Cortisol	3.4 ± 0.15	3.37 ± 0.13	3.24 ± 0.16	$0.593_{1,21}$	0.557
Mean (SEM) (pg/ml)					
IFN-ɣ	0.93 ± 0.14	1.00 ± 0.13	1.10 ± 0.12	$1.016_{1,7}$	0.384
IL-17	0.8 ± 0.03	0.9 ± 0.06	0.85 ± 0.04	$2.502_{1,15}$	**0.099**
IL-2	1.62 ± 0.1	1.77 ± 0.1	1.83 ± 0.1	$0.618_{1,7}$	0.555
IL-4	1.62 ± 0.1	1.77 ± 0.1	1.83 ± 0.1	$3.83_{1,17}$	**0.032**
IL-6	1.5 ± 0.1	1.6 ± 0.1	1.52 ± 0.1	$0.808_{1,17}$	0.454
MCP1	4.35 ± 0.15	3.92 ± 0.19	4.27 ± 0.17	$4.221_{1,15}$	**0.024**
TNF-α	1.17 ± 0.08	1.22 ± 0.09	1.17 ± 0.1	$0.134_{1,17}$	0.875

A repeated measures ANOVA showed that drumming significantly increased the anti-inflammatory cytokine IL-4 ($F_{2,34}$=3.830, p<0.05). Planned polynomial contrasts showed that there was a linear effect across time ($F_{1,17}$=6.504, p<0.05) (see Figure 6A). Alongside this, there was a significant change in levels of the pro-inflammatory chemokine MCP-1 ($F_{2,30}$=4.221, p<0.05), which polynomial contrasts revealed to be a quadratic effect, with an initial increase followed by a return to near baseline levels ($F_{1,15}$=10.793, p<0.01) (see Figure 6B). There was also a near-significant effect for IL-17 ($F_{2,30}$=2.502, p=0.099), also shown to be a quadratic effect characterized by an initial increase followed by a small decrease ($F_{1,15}$=4.301, p=0.056) (see Figure 6C). No changes were found in levels of TNF-α across the 10 weeks ($F_{2,34}$=0.134, p=0.875) nor IL-6 ($F_{2,34}$=0.808, p=0.454), and although there was a decrease in cortisol across the 10 weeks, this was not significant ($F_{2,42}$=0.593, p=0.557). However, due to difficulties in analysing these samples, many results were outside the limits of detection accounting for the smaller sample size in the statistical analysis.

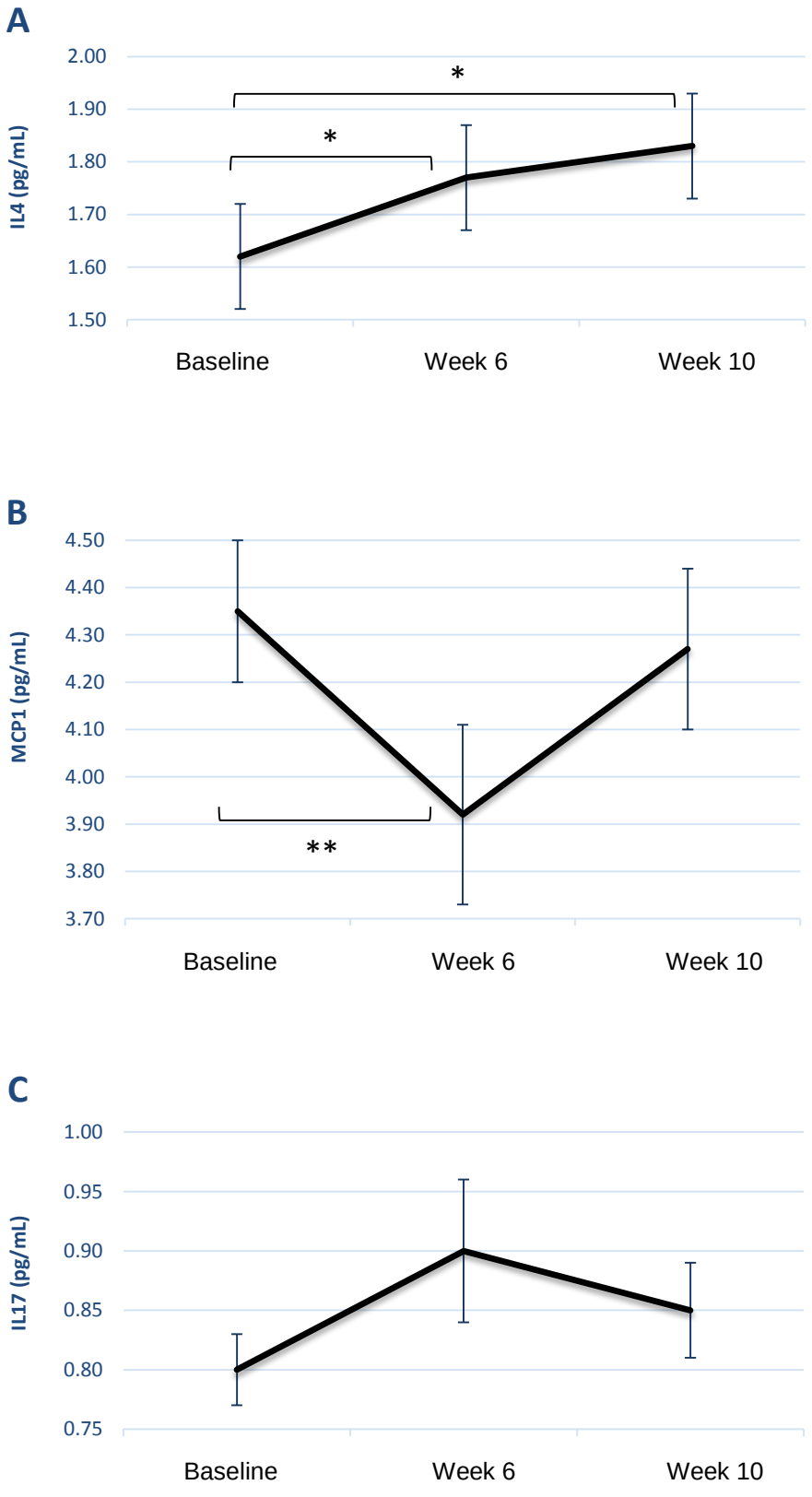


*Fig 6. Mean cytokines levels (with standard errors) in response to drumming across the 10 weeks for (A) interleukin 4 (IL4), (B) monocyte chemoattractant protein 1 (MCP1), and (C) interleukin 17 (IL17). * = p<.05, ** = p<.01.*

A further comparison of pro- versus anti-inflammatory response was calculated by comparing levels of the cytokines TNF-α (pro-inflammatory) and IL-4 (anti-inflammatory) with standardized scores. At baseline, a comparison of levels of TNF-α and IL-4 was elevated towards TNF-α (a pro-inflammatory response); however, over the intervention period, there was an increasing prominence of IL-4 (an anti-inflammatory response) which reached significance by week 6 (t_{16}=-2.193, p<0.05) (see Figure 7).

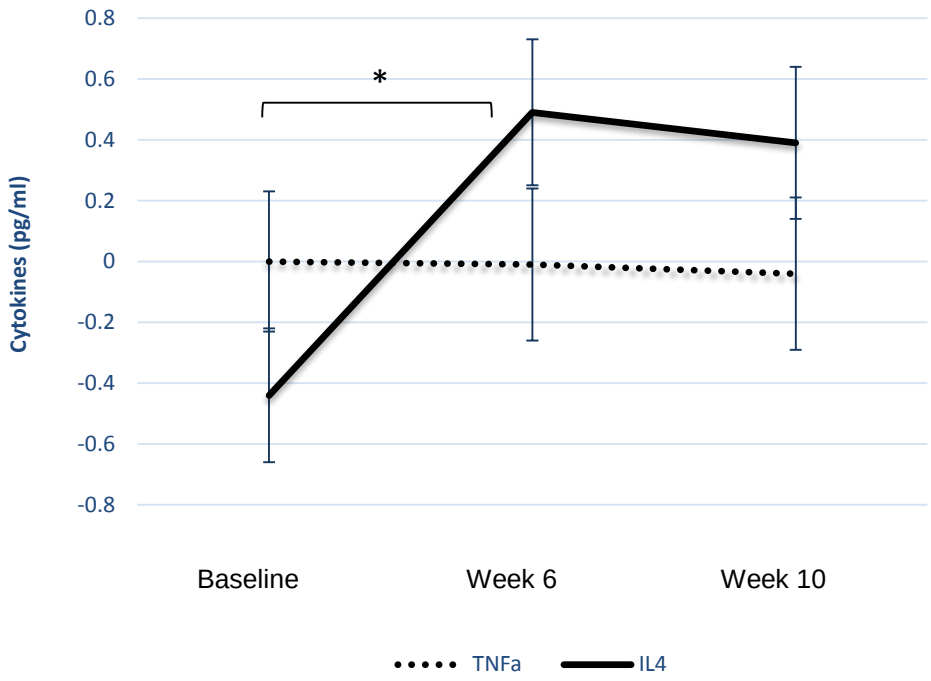


Fig 7. Mean Z scores of TNF-α and IL-4 (with standard errors) in response to drumming across the 10 weeks

However, using either the stricter or more lenient Bonferron correction, none of the biological results would have maintained significance.

4.3.4 Interactions

In addition to pre-post testing, we also undertook more exploratory analyses of the interactions between psychological and biological response. There were no correlations between any psychological changes across the 10 weeks and baseline age, educational attainment and current or previous musical experience. However, there was a negative correlation between

baseline wellbeing and change in wellbeing across the 10 weeks (r=-.414, p=.006), baseline anxiety and change in anxiety (r=-.558, p<.001), baseline depression and change in depression (r=-.714, p<.001) and social resilience (r=-.484, p=.001), showing that participants with worse mental health benefited the most from involvement in the project.

In the drumming group, there was a negative correlation between changes in IL4 and changes in anxiety across the 10 weeks, with decreases in anxiety associated with increases in IL4 (r=-.398, p=.044) and a near-significant negative correlation between changes in IL17 and changes in social resilience (r=-.381, p=.080).

When comparing baseline levels with change scores across the 10 weeks, no correlations were found between baseline psychological levels and changes in biomarkers. However, there was a positive correlation between baseline IL17 levels and changes in wellbeing, with higher baseline IL17 associated with greater improvements in wellbeing (r=.469, p=.028). No other correlations beween baseline biological levels and psychological changes were found.

4.4 Discussion

The aim of this study was to extend and further explore the results noted in study 1 and to try to assess whether a music intervention (group drumming) could produce improvements in mental health and reduce inflammatory responses over several weeks and, as such, whether music is a promising psychosocial intervention for mental health service users.

We hypothesized that across the ten-week intervention there would be a decrease in symptoms of depression and anxiety and improvements in social resilience and mental wellbeing. This was demonstrated by significant reductions in HADSD and significant increases in CDRISC, both of which held when controlling for multiple comparisons using a clustered (more lenient) Bonferroni correction, with HADSD holding when a stricter correction was applied. There were also significant improvements in anxiety and near-significant improvements in WEMWBS compared with the control group, but neither of these held when controlling for multiple

comparisons. We also hypothesized that the changes seen in the drumming group would be maintained at 3-month follow-up, which was also confirmed. Furthermore, for the drumming group, we tested whether there would be a decrease in pro-inflammatory cytokine activity. Although there was no clear decrease in pro-inflammatory activity, the results showed a significant increase in the anti-inflammatory cytokine IL-4 and a shift towards an anti-inflammatory profile, as shown by the balance between levels of TNF-α and IL-4. However, when controlling for multiple comparisons, these results did not hold, attesting to the exploratory nature of the findings. It remains to be seen whether such results would have achieved more robust statistical results with a larger sample size. This issue will be returned to in study 4.

This study supports the findings of study 1 by demonstrating that drumming leads to improved psychological states, specifically depression and social resilience, across six weeks compared with a control group. Although mental wellbeing, which showed a significant increase in the preliminary study, was not significant at six weeks when the control group was added in this current study, it showed a similar pattern of increase, and when the current study was extended to ten weeks this increase moved towards significance. Overall, this demonstrates improved psychological state in the drumming but not the control group across multiple related constructs attesting to the efficacy of group drumming in improving mental wellbeing.

Furthermore, although in both the preliminary study and the current study the decrease in anxiety did not reach significance across the first six weeks, when the drumming was extended to 10 weeks significance was reached. These findings are parable with findings from previous music studies involving anxiety and depression, such as Coulton et al. (2015) who also found significant improvements across 3 months of group singing in older adults and Erkkila et al. (2011) who found significant improvements across 3 months of individualised music therapy with patients with depression (4). However, both studies found that results returned to near baseline levels (producing non-significant results compared to baseline) at follow-up 3 months following the end of the music intervention. In comparison, this study found that results were

maintained for 3 months following the end of the intervention. It remains unknown whether even longer interventions could further improve outcomes; however, given funding limitations for community interventions (30), it is promising that just 10 weeks have been shown to lead to results being maintained for three months after the end of the intervention.

A key finding of this study was that drumming led to increases in anti-inflammatory activity, shown in IL4 as well as in the ratio of TNFα (pro-inflammatory) to IL4 (anti-inflammatory). This finding is different from the preliminary study in which decreases were found in IL-6, MCP-1, IFN-ɣ and TNF-α, suggestive of a reduction in pro-inflammatory response. This study found some parallel results, such as a reduction in MCP-1 levels by week 6. However, it also suggested that these results may not be maintained. Nevertheless, both studies show evidence of a rebalancing of pro- vs anti-inflammatory response. In study 2, the intervention led to increases in the anti-inflammatory cytokine IL-4, both between weeks 1 and 6 and continuing to week 10. This, and the increasing levels of IL-4 both in its own right and relative to TNF-α suggests an overall bias towards an anti-inflammatory response. These results are in line with the reductions in pro-inflammatory response but not anti-inflammatory response found in study 1. They also chime with theories of Dahl et al. (2014) who suggested that measurable improvements in mental health occur alongside shifts towards an anti-inflammatory response. Furthermore, as TNF-α and IL-4 are also markers of Th1 and Th2 pathways respectively, this study demonstrates a shift away from Th1 responses in favour of Th2 responses, which is in line with previous studies demonstrating a direction of shift in patients recovering from depression (Kubera et al., 2001; Myint, Leonard, Steinbusch, & Kim, 2005, p. 2).

A point of note is that, due to extending the upper limit of mental health severity and removing the cap on HADS scores used in study 1, the participants in study 2 were of slightly worse mental health. In fact, a one-way analysis of variance showed that the two study samples differed significantly in terms of baseline depression scores and social resilience scores:

Table 17. Psychological profile of participants in studies 1 and 2 at baseline

Scale	Study 1	Study 2	F	p
Mean[a] (SD)				
HADSA	9.33 ± 4.19	11.03 ± 5.2	$1.937_{1,58}$	0.169
HADSD	6.27 ± 3.38	8.90 ± 5.0	$5.619_{1,58}$	**0.021**
CD-RISC	60.32 ± 16.47	46.93 ± 22.1	$7.165_{1,59}$	**0.01**
WEMWBS	44.55 ± 11.11	39.61 ± 11.3	$2.861_{1,58}$	0.096

Consequently, although the psychological findings from study 2 are very similar to those from study 1, they cannot be used as a direct comparison. This also has implications for the biological results. It is possible that some of the nuances in biological response between the two studies could perhaps be due to differences in baseline depression levels. Beyond this, there were also some challenges with analysing the samples for this study. Many of the samples, particularly for IL-2 and TGF-β, fell outside levels of detection. Variability in levels within the samples was also high. This meant that some results were low on statistical power. Although samples were stored, transported and analysed in the same way, studies 2 and 3 were analysed separately from study 1 so minor deviations in terms of the sample handling could have led to these discrepancies between batches.

In study 1, we hypothesised that stress was a key mediator in the cytokine response found across the drumming intervention. However, no significant changes were found for the Perceived Stress Scale in this study. While this remains to be explored in more detail, given the stronger improvements found for social resilience, it is possible that the social elements of group drumming had more of an influence on biological response than psychological stress reduction. This would be in keeping with more general theories on the strong social interactions involved in music and the possible biological underpinnings of these (Dunbar, 2003; Huron, 2001; Tarr, Launay, & Dunbar, 2014), and the influence of social support on immune function (Baron, Cutrona, Hicklin, Russell, & Lubaroff, 1990; Cohen, 1988; Fagundes, Gillie, Derry, Bennett, & Kiecolt-Glaser, 2012; Hicks, 2014; Uchino, Cacioppo, & Kiecolt-Glaser, 1996).

This study was quasi-experimental, and as such, due to the logistics of recruitment, participants were not randomised. Furthermore, despite recruiting through the same channels with the same inclusion criteria for both the drumming and control group, control participants had lower depression scores at baseline than the drumming group. Due to financial constraints, it was also not possible to analyse biological samples from controls, which is a limitation to interpreting these findings. Although all other psychological and demographic measures were matched, a future randomised study would help to confirm results. Future studies could also benefit from including comparison as well as control groups in order to assess which features of the drumming interention (whether physical, social or otherwise) are responsible for changes.

In conclusion, this study replicates study 1 demonstrating that group drumming can reduce depression and anxiety and improve social resilience and mental wellbeing in mental health service users over a 6 and 10-week span. Changes in psychological profiles are underpinned by reductions in inflammatory response and a shift towards an anti-inflammatory immune profile. This extends our evidence as to the psychobiological mechanisms of group music-making interventions and highlights their longitudinal impact, both opening new avenues for research and highlighting the practicality and potentially cost-effectiveness of community music interventions for mental health patients.

5 STUDY 3

5.1 Introduction

The results from studies 1 and 2 explore the impact of group drumming on psychological and biological response. However, as the intervention was analysed as a single entity, it remains unknown exactly why the intervention led to these responses.

In the initial literature review at the start of this PhD, it was suggested that four separate factors could influence psychoneuroimmunological response to a music intervention: aural, personal, social and physical. Indeed, given growing research demonstrating the impact of physical activity, social engagement and music on immune function (Fancourt et al., 2014; Gleeson, 2007; Uchino, 2006), one theory is that specific components of group drumming were responsible for changes in psychological and biological response.

However, study 1 also showed that across a single hour, participants experienced changes in emotional responses as well as cortisol and cytokine levels. Within the field of psychobiology, there is a growing literature showing how emotions are interlinked with biological processes. For example, a number of studies have looked at the biological correlates of positive state emotions, such as increases in levels of the antibody salivary immunoglobulin A (Dillon, Minchoff, & Baker, 1985; Harrison et al., 2000; Hucklebridge et al., 2000), some preliminary evidence of changes in leukocytes including increases in natural killer cells and circulating B-cells and T-cells (Berk, Felten, Tan, Bittman, & Westengard, 2001; Futterman, Kemeny, Shapiro, & Fahey, 1994) and changes in cytokine levels such as increases in interleukin 2 and 3 and decreases in tumour necrosis factor alpha (TNF-α) (Berk et al., 2001; Mittwoch-Jaffe, Shalit, Srendi, & Yehuda, 1995). Over time, positive trait effects have been shown to correlate with lower inflammatory markers (Andrew Steptoe, Demakakos, de Oliveira, & Wardle, 2012) and lower cortisol awakening response (Dockray & Steptoe, 2010; Endrighi, Hamer, & Steptoe, 2011; Andrew Steptoe, O'Donnell, Badrick, Kumari, & Marmot, 2008). Conversely, work has also been carried out on the impact of negative emotions on biology. State hostility has been shown to

decrease functional immune parameters (Kiecolt-Glaser et al., 1993), the emotional state of shame to increase cortisol and pro-inflammatory cytokine response (Dickerson, Gruenewald, & Kemeny, 2004) and stress to increase natural killer cells and pro-inflammatory cytokines (Segerstrom & Miller, 2004). Longitudinally, negative traits such as depression have been shown to correlate with higher inflammatory markers (Dahl et al., 2014; Raison & Miller, 2011) and flattened diurnal cortisol curves (Du et al., 2014). Consequently, an alternative theory is that drumming led to changes in emotions with subsequent biological responses.

Consequently, study 3 aimed to ascertain whether the specific act of group drumming led to a greater modulation in emotion than control conditions (PhD hypothesis 5) and whether biological underpinnings to such a response were due to these emotions (PhD hypothesis 6), or whether biological response to drumming was instead a result of the physical components involved in the activity. The drumming intervention was replicated and three control conditions were created to be studied alongside it, each missing a crucial element of the drumming condition (see Table 18). The drumming condition was identified to contain four key components: the physical act of drumming, the visual display of watching people drum, the sound of the drumming and the social element of being in a group situation. In control 1, participants watched a performance of drumming by four drummers, thereby experiencing the same visual, musical and social elements but not the physical element of drumming themselves. In control 2, participants listened to a performance of drumming on speakers, thereby hearing the same musical elements in the same social setting but neither seeing any drumming nor physically moving themselves. In control 3, participants listened to audio stories on speakers, thereby experiencing the same social setting and having some form of auditory stimulation, but not receiving any of the musical, visual or physical stimulus of the other conditions.

We hypothesised that (1) group drumming would lead to a greater change in self-reported emotion than control interventions; (2) there would be differences in biological measures between group drumming and the control activities related to physical parameters of the

drumming intervention; and (3) there would be an interplay between emotion and biological response to group drumming. Our study contained two phases: a between-person and a within-person design to investigate these issues.

Table 18. Components of the experimental and control conditions

DESIGN	NAME	CORE COMPONENTS				
		Physical	Visual	Music	Social	
Experimental	Drumming	✓	✓	✓	✓	participants joined in call-and-response exercises and learnt drumming patterns that built up into larger pieces.
Control 1	Watching		✓	✓	✓	participants watched a performance by the professional drummer and three students involving call-and-response exercise and larger drumming pieces
Control 2	Listening			✓	✓	participants listened to audio recordings of call-and-response exercises and larger drumming pieces
Control 3	Audio control				✓	participants listened to audio stories about African culture surrounding drumming

5.2 Methods

5.2.1 Participants

Twenty-five participants were initially recruited to each group in the study totalling 100 participants (see Figure 8). Mental health service users were recruited using the same criteria and channels as in studies 1 and 2 (but with no cut-off on HADS).

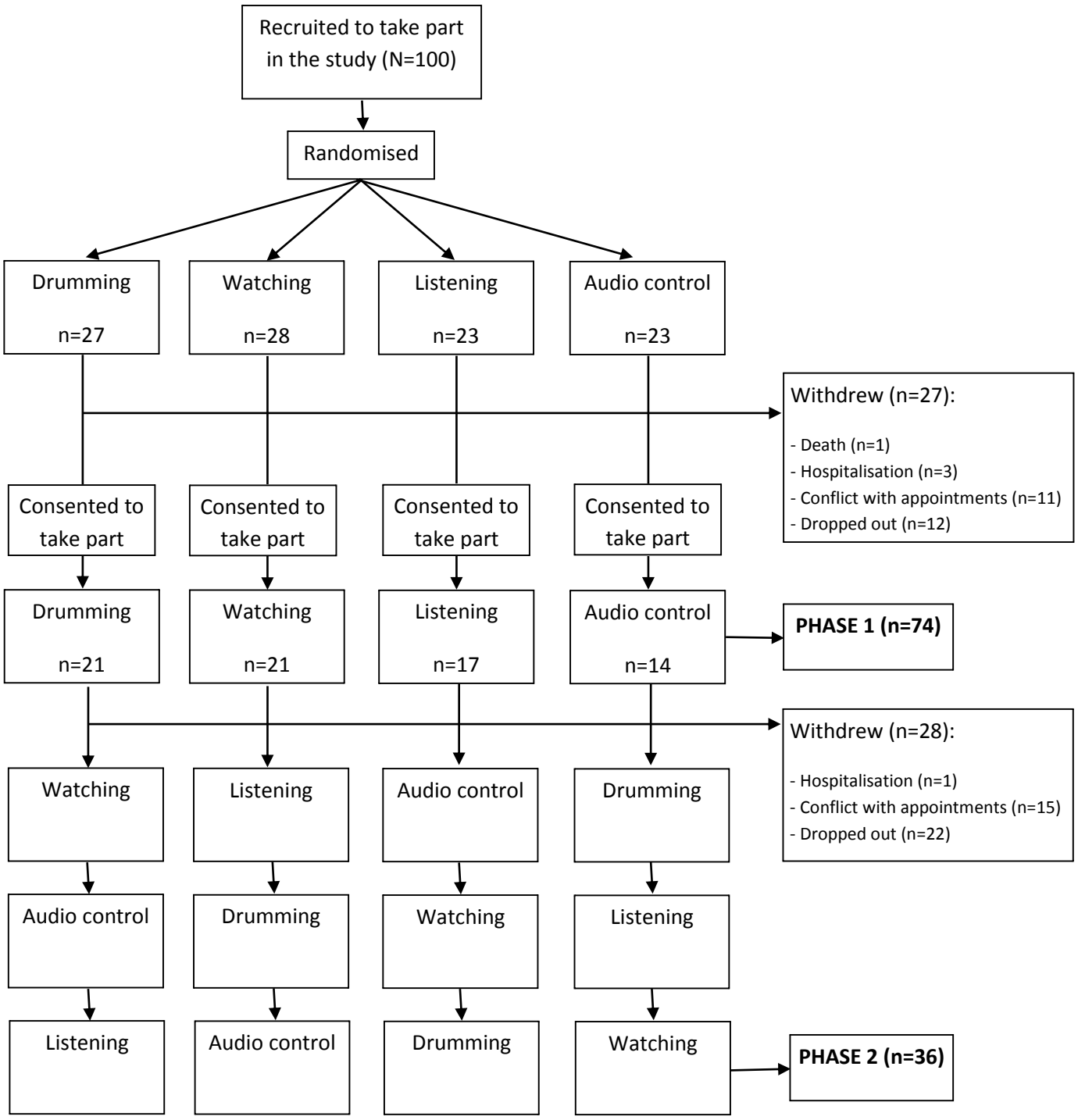


Fig 8. Participant recruitment to study 3

5.2.2 Design and procedure

Participants were informed that they would be taking part in a creative activity around the theme of drumming. Sessions ran on weekday mornings in a hired community space in London, led by a professional drummer and supported by three students from the Royal College of Music. In order to minimise extraneous sources of variability all four conditions took place in the same space led by the same musicians. All sessions lasted 60 minutes. The quantity of talking in each

session either introducing the pieces of music or audio stories was fixed to 20% of the 60-minute session time. The participants sat in the same circular arrangement for each condition.

PHASE 1

Phase 1 aimed to assess reactions to each of the four activities on a between-person basis. Following recruitment, participants were randomised using blocked randomisation stratified by gender. Twenty-seven participants withdrew prior to participation in the study leaving seventy-three remaining participants**.**

PHASE 2

Data from the initial drumming study suggested that results across the first session of a specific music activity were less clear than across subsequent sessions, perhaps due to anxiety in the first session. A first session may also lead to greater responses due to a Hawthorne effect. Consequently, following participation in the session for phase 1, participants were given the option of returning for a further 3 weeks, during which time they would experience each of the other three activities. Thirty-six participants consented to take part in the within-person phase 2 study**.**

No significant differences were found between this group and the wider group from phase 1 in terms of age, gender or psychological profile. To control for order effects, the order of the activities was randomised so each one appeared in the 1st, 2nd, 3rd and 4th week in one or other of the groups (see Table 19)**.**

Table 19. Order of interventions in phase 2

	Group 1	Group 2	Group 3	Group 4
Week 1	Drumming	Watching	Listening	Audio
Week 2	Watching	Listening	Audio	Drumming
Week 3	Audio	Drumming	Watching	Listening
Week 4	Listening	Audio	Drumming	Watching

5.2.3 Demographic data

Participants' socio-demographic and health characteristics were obtained at baseline by means of a set of self-administered questionnaires including the Hospital Anxiety and Depression Scale (HADS), the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS), and the Connor-Davidson Resilience Scale (CD-RISC). These measures were described in section 3.2.3.

5.2.4 Emotion measures

Immediately before and after each individual session, participants completed visual analogue scales (VAS) to measure 12 emotional states: afraid, angry, anxious, confused, connected, energetic, happy, relaxed, sad, stressed, tense and tired. Participants placed a mark on a 100mm line labelled from 'not at all' to 'very' for each construct and the distance was measured from left to right with higher values indicating greater intensity of the state being measured (Wewers & Lowe, 1990).

5.2.5 Appraisal measures

Visual analogue scales were also used to measure the connotative meaning of each activity using semantic differential ratings; bipolar psychometrically controlled scales (Saider & Osgood, 1969). Immediately after each individual session, participants were asked to rate how they found it on three binary scales: one assessing activity (boring-stimulating), one assessing potency (meaningless-meaningful) and one assessing evaluation (unpleasant-enjoyable).

5.2.5 Biological measures

Saliva samples were gathered before and after each session and analysed using multiplex assays for the same biomarkers as studies 1 and 2 to enable consistent comparison: cortisol, IL-2, IL-4, IL-6, IL-17, IFN-ɣ, TNF-α, TNF-β and MCP-1. An overview of the role of each biomarker can be found in Appendix 1.

5.2.6 Statistical analyses

A power calculation carried out using the VAS 'happiness' measure from study 1 showed that with an alpha of 0.05 and power of 0.8, 15 participants were needed per group. Although this

study includes a range of markers, happiness was selected as the outcome to focus on for statistical purposes as it provided clear responses in study 1. As a result, 25 participants were recruited into each condition to allow for drop-outs. Biological measures were not designed to be powered for group comparisons so were treated as exploratory data.

Statistical analysis was performed using SPSS (Version 22.0, SPSS Inc., USA). For preliminary analyses for both phases 1 and 2, we used paired T-tests to compare the change in psychological responses pre-to-post each session. More comprehensive statistical tests were undertaken for each phase as follows:

Phase 1: For psychological and biological measures to test hypotheses 1 and 2, we used repeated measures analyses of variance (ANOVAs) to test changes across time (pre vs post each session) and between group with post hoc tests. For activity appraisals, we used one-way analyses of variance with post-hoc tests using Games-Howell correction due to inequality of variance. To test hypothesis 3 we carried out correlations between psychological and biological measures using Pearson's product-moment correlation coefficient. Where correlations were significant we carried out linear regression models with biomarkers as the independent variable, emotions as the dependent variable, with gender and age as planned covariates.

Phase 2: For psychological and biological measures to test hypotheses 1 and 2, we used 2 x 4 repeated measures analyses of variance (ANOVAs) to test changes across time (pre vs post each session) and between the four conditions with planned within-subject contrasts. For activity appraisals, we used a repeated measures ANOVA to test between conditions with post hoc tests. To test hypothesis 3 we carried out correlations between psychological and biological measures using Pearson's product-moment correlation coefficient. Where correlations were significant we carried out linear regression models with biomarkers as the independent variable, emotions as the dependent variable, with gender and age as planned covariates.

For biological data, where the distribution of cytokines was positively skewed, data were logarithmically transformed prior to analysis. Some samples were unsuitable for analysis or levels fell below the limit of detection, and so these were excluded and the degrees of freedom adjusted accordingly.

For both phases, corrections for multiple comparisons were made using Bonferroni's correction. Corrections were applied separately to phases 1 and 2 as they had different study designs. At the strictest level, a total of 108 pre-post tests were carried out across each phase, meaning an $\alpha<.0005$ would be required for significance. However, the T tests were only intended to be very exploratory rather than formally be part of the analyses. The ANOVAs were the key way that change across time and between group was assessed, and at the time of the study design it was these that were chosen as the main analyses. So if we adjusted just based on the core ANOVAs, an $\alpha<.002$ would be required for each phase. More leniently, if we clustered results into category of data, an $\alpha<.004$ would be required for psychological tests in each phase, an $\alpha<.006$ for biological tests, and an $\alpha<.017$ for semantic differentials.

5.3 Results and discussion

5.3.1 Phase 1: Demographic data

Table 20. One-way analysis of variance showing group differences in participant demographics in phase 1

	Experimental drumming	Control 1 watching	Control 2 listening	Control 3 audio control	p
N	21	21	14	17	
Gender (male)	33.3%	28.6%	28.6%	41.2%	0.843
Age (SD)	51.24 (16.5)	55.95 (16.0)	37.15 (12.9)	48.00 (10.3)	**0.005**
Ethnicity (white)	71.4%	81%	57.1%	58.8%	0.367
HADSA (SD)	11.68 (5.4)	9.95 (4.6)	11.71 (4.9)	10.53 (5.5)	0.667
HADSD (SD)	6.63 (4.7)	7.35 (4.4)	7.29 (4.6)	8.67 (4.7)	0.638
WEMWBS (SD)	41.11 (11.2)	42.80 (10.2)	41.43 (5.8)	39.27 (12.4)	0.799
CDRISC (SD)	53.79 (24.5)	58.50 (20.1)	55.86 (12.6)	53.47 (29.0)	0.898

Most of the participants were white females. Participants showed baseline anxiety levels consistent with mild to moderate distress (mild, 8-10; moderate 11-14), and mild depression levels (Zigmond & Snaith, 1983). Mental wellbeing levels on the WEMWBS were at the low end of average results (40-59) (Tennant et al., 2007) and social resilience scores were considerably lower than the general population (80.7) and also lower than either psychiatric outpatients or those with generalised anxiety disorder (68 and 62.4 respectively) (Connor & Davidson, 2003).

Participants in all four groups were well matched at baseline in gender, ethnicity and psychological profile. However, there was a significant difference in age, with the listening control having a lower average than the other conditions, and significantly lower than the watching control. This appears to be a chance effect. However, age was factored into regression analyses to mitigate these effects.

5.3.2 Phase 1: Emotion results

At baseline, there were no differences in emotion scores between the four conditions. Preliminary exploratory T tests showed that drumming led to significant changes in eight of the twelve emotions assessed: decreases in anger ($t_{(20)}$=-2.929, p=.008), anxiety ($t_{(20)}$=-3.722,

p=.001), confusion ($t_{(20)}$=-2.792, p=.011), sadness ($t_{(20)}$=-2.335, p=.03), and tension ($t_{(20)}$=-2.709, p=.014) and increases in connectedness ($t_{(20)}$=2.632, p=.016), energy ($t_{(20)}$=2.118, p=.047), and relaxation ($t_{(20)}$=4.354, p<.001), with all bar sadness and energy holding when adjusted for multiple comparisons. By comparison, there were no significant changes in the watching condition. In the listening condition, there was a decrease in fear ($t_{(12)}$=-2.321, p=.039) and an increase in relaxation ($t_{(20)}$=3.156, p=.008), but these did not hold when adjusting for multiple comparisons. In the audio control condition, there were changes in five emotions: decreases in anxiety ($t_{(20)}$=-2.878, p=.011), stress ($t_{(20)}$=-3.387, p=.04) and tension ($t_{(20)}$=-3.978, p=.001) and increases in relaxation ($t_{(20)}$=2.872, p=.011) as well as connectedness ($t_{(16)}$=2.478, p=.025) (see Table 21). When controlling for multiple comparisons at the strictest level (which included these T tests), drumming still led to increases in relaxation.

When comparing the activities against one another, overall ANOVAs were non-significant across the four activities. However, we conducted some exploratory univariate ANOVAs between drumming and the audio control condition which gave preliminary indications that drumming led to greater change than the audio control condition: participants reported feeling significantly more energetic after drumming compared to the audio control ($F_{1,36}$=4.619, p=0.039) and there was a near-significant effect on happiness ($F_{1,37}$=3.465, p=.071). However, exploratory comparisons between the drumming condition and the other control conditions showed non-significant effects, suggesting that both the watching and listening conditions had an effect midway between the drumming and the audio control conditions (albeit nonsignificant). This suggests that music provided some level of alteration, but the physical component of drumming (only found in the experimental condition) was key in the alteration of emotions for this intervention. These results should be interpreted with caution given their exploratory basis.

Table 21. Changes in emotion in response to group drumming and each of the three control conditions

	Drumming				Watching				Listening				Audio			
	Baseline	Mean change[b]	SD	p[a]	Baseline	Mean change	SD	p[a]	Baseline	Mean change	SD	p[a]	Baseline	Mean change	SD	p[a]
Afraid	23.81	-7.286	17.746	.075	27.05	-6.000	27.197	.324	22.93	-14.000	21.752	**.039**	30.12	-10.000	19.887	.055
Angry	24.43	-9.619	15.051	**.008**	26.00	-4.667	18.882	.271	14.42	-3.636	25.621	.648	27.94	-8.471	22.864	.146
Anxious	43.19	-19.571	24.099	**.001**	41.43	1.350	38.805	.878	46.71	-1.769	23.015	.786	54.69	-22.563	31.356	**.011**
Confused	27.48	-9.143	15.008	**.011**	31.76	-6.238	19.766	.164	18.92	-7.333	16.999	.163	31.12	- 0.647	30.488	.931
Connected	46.00	18.048	31.427	**.016**	60.67	5.190	24.631	.346	42.71	20.308	32.806	**.045**	33.18	11.000	18.303	**.025**
Energetic	51.43	11.667	25.243	**.047**	53.86	5.500	24.712	.332	48.50	-3.154	13.849	.428	40.44	1.000	26.917	.884
Happy	53.29	10.762	25.434	.067	56.85	2.263	24.131	.688	47.07	8.769	14.901	.055	40.00	3.941	28.556	.577
Relaxed	48.95	21.714	22.854	**<.001**	55.00	11.810	32.306	.109	44.29	25.000	28.557	**.008**	33.65	23.471	33.690	**.011**
Sad	32.57	-7.476	14.675	**.030**	32.29	-7.286	18.588	.088	37.71	-14.385	27.921	.088	41.00	-6.647	29.967	.374
Stressed	41.29	-7.900	32.267	.287	51.57	-11.500	40.689	.222	45.36	-19.154	33.022	.058	51.00	-18.941	23.056	**.004**
Tense	40.29	-12.905	21.831	**.014**	39.95	-1.700	35.630	.833	44.57	-14.000	29.172	.109	51.00	-24.353	25.239	**.001**
Tired	31.71	-1.100	29.658	.870	48.52	-4.900	38.059	.572	48.64	-2.583	26.794	.745	48.47	0.882	31.535	.910

Notes: SD: standard deviation

[a]P values shown. The Bonferroni adjustment is α<.0005.

[b]Mean change score across the intervention

5.3.3 Phase 1: Activity appraisal results

Participants were also asked to appraise how they experienced the four activities (see Figure 9). Results showed significant differences in terms of how stimulating ($F_{3,69}$=6.081, p=0.001), meaningful ($F_{3,69}$=4.739, p=0.005) and enjoyable ($F_{3,70}$=5.332, p=0.002) participants found them. Post-hoc tests demonstrated specifically that the drumming intervention was significantly more stimulating than the audio control (p=.001), more meaningful than the audio control (p=.017) and more enjoyable than both the audio control (p=.011) and the watching condition (.046). The physical act of drumming did not, however, differ from listening.

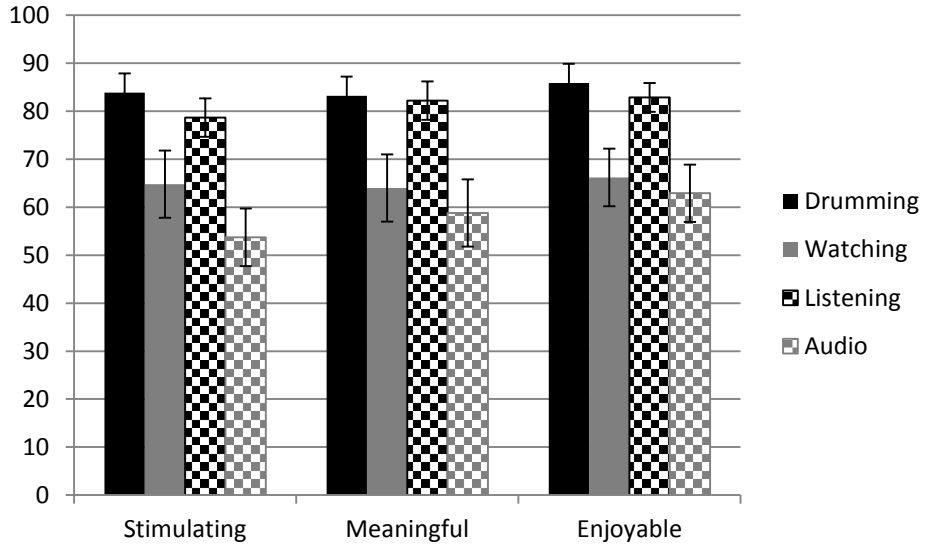


Fig 9. Mean appraisals (with standard error) of each condition for phase 1

There were also significant correlations between changes in perceived happiness levels and how stimulating, meaningful and enjoyable participants found the activities, with happiness change showing a small correlation with how stimulating a participant found an activity (R=.255, p=.037), how meaningful they found it (R=.281, p=.021) and how enjoyable they thought it was (R=.237, p=.05). When controlling for multiple comparisons at the strictest level, no comparisons held. However, at the mid-level (which was the planned level of testing at the start of the study), the differences in enjoyment and stimulation held; and at the most lenient level all three held.

5.3.4 Phase 1: Biological results

Response in biomarkers to the different conditions are shown in Table 22**.** A number of samples fell below levels of detection which accounts for the small sample sizes in some of the groups. Paired T tests showed that from before to after the drumming session, there were no significant changes found. In the watching condition, there were reductions in IL-2 ($t_{(8)}$=-2.325, p=.049) and IL-4 ($t_{(18)}$=-2.823, p=.011). In the listening condition, there was a significant increase in MCP-1 ($t_{(9)}$=2.524, p=.033). In the audio control there were significant decreases across time in both IL-2 ($t_{(10)}$=-3.234, p=.009) and IL-4 ($t_{(15)}$=-3.405, p=.004). When controlling for multiple comparisons using the strictest Bonferroni which included T tests, nothing held.

To test hypothesis 2, that there were differences in biological measures between group drumming and the control activities, comparisons were made between the four conditions. No significant differences were found. However, retrospective power calculations showed that, due to the small sample sizes in each condition, there was not sufficient power to undertake comparisons between the four activities.

Table 22. Changes in biomarkers in response to group drumming and each of the three control conditions

	Drumming				Watching				Listening				Audio			
	Baseline[c]	Mean change[b]	SD	p[a]	Baseline	Mean change	SD	p[a]	Baseline	Mean change	SD	p[a]	Baseline	Mean change	SD	p[a]
IL-2	2.89 (7)	-0.301	0.53	.588	5.44 (9)	-1.22	0.53	**.049**	6.01 (2)	1.182	2.05	.565	3.89 (11)	-1.835	1.88	**.009**
IL-4	1.84 (16)	-0.223	0.010	.051	1.96 (19)	-0.231	0.08	**.011**	1.91 (10)	-0.162	0.85	.560	1.73 (16)	-0.300	0.35	**.004**
IL-6	1.65 (16)	-0.195	0.010	.074	1.52 (20)	-0.035	0.08	.673	1.54 (9)	0.068	0.60	.572	1.51 (16)	-0.156	0.38	.462
IL-17	1.05 (13)	-0.108	0.08	.218	0.97 (17)	-0.040	0.06	.482	0.81 (9)	0.079	0.45	.614	0.89 (1)	-0.002	0.25	.975
Cortisol	3.02 (17)	0.004	0.15	.976	2.83 (21)	0.004	0.18	.984	3.01 (10)	0.126	1.44	.788	3.43 (17)	-0.025	0.56	.856
IFNg	1.24 (8)	-0.064	0.14	.670	1.31 (9)	-0.266	0.13	.083	0.84 (4)	0.155	0.30	.379	1.05 (7)	0.063	0.37	.668
TNFa	1.34 (14)	-0.023	0.08	.782	1.38 (18)	0.171	0.10	.112	0.84 (8)	0.597	1.19	.199	1.09 (14)	0.144	0.50	.302
TGFb	2.38 (4)	0.986	0.95	.376	3.10 (6)	-1.116	0.69	.168	2.84 (2)	0.450	2.38	.834	2.67 (6)	-0.363	2.01	.677
MCP1	4.19 (16)	0.307	0.17	.086	4.54 (20)	0.165	0.13	.211	3.60 (10)	0.781	0.98	**.033**	4.05 (16)	0.132	0.95	.588

Notes: SD: standard deviation

[a]P values The Bonferroni adjustment is α<.0005

[b]Mean change score across the intervention

[c]The number of detectable samples per group is given in brackets.

To test hypothesis 3, that participants' biological response to the different interventions was associated with changes in emotion rather than specific parameters of the interventions themselves, correlations were run between changes in biomarkers and changes in emotions. Significant correlations were found for cortisol, IFN-ɣ and TNF-α. A linear regression model showed that changes in cortisol were associated with 9% of the variance in changes in sadness with adjustments for age and gender (B=-.01, SEM=.004, $t_{(63)}$=-2.353, p=.022) with increases in cortisol indicative of a stimulation response found alongside decreases in sadness. Another linear regression showed that changes in TNF-α accounted for 10% of the variance in how afraid participants reported feeling (B=-.008, SEM=.004, $t_{(52)}$=-2.063, p=.044) with increases in TNF-α found alongside decreases in fear.

Linear regressions also showed that IFN-ɣ was associated with between 28% and 34% of the variation in perceived tension, relaxation, psychological stress and feelings of connectedness with increases in IFN-ɣ leading to decreases in negative states (tension and stress) and increases in positive states (relaxation and connectedness) (see Table 23)**.** However, sample sizes for these calculations were lower than usual for regression models so results should be interpreted with appropriate caution.

Table 23. Regression of changes in IFN-ɣ on subjective emotion responses

	B	SEM	t (n)	P	R^2
Tense	-.005	.002	-2.146 (26)	.043	.275
Relaxed	.005	.002	2.118 (27)	.045	.290
Stressed	-.007	.003	-2.248 (25)	.035	.313
Connected	.007	.003	2.588 (27)	.016	.341

5.3.5 Phase 2: Demographic data

Participants who chose to remain in the study for phase 2 did not have any significant baseline differences from those who dropped out.

Table 24. Demographics of participants in phase 2

	Participants (N=36)
Gender (%)	
Male	10 (28)
Female	26 (72)
Age (SD)	52.4 (18.2)
Ethnicity (%)	
White	28 (78%)
Black	3 (8%)
Asian	3 (8%)
Other	2 (6%)
HADS (SD)	
Anxiety	10.64 (5.1)
Depression	6.53 (4.1)
WEMWBS (SD)	42.08 (14.7)
CDRISC (SD)	58.55 (20.0)

Most of the participants were white females. Participants showed baseline anxiety levels consistent with mild to moderate distress (mild, 8-10; moderate 11-14), and sub-clinical depression levels (Zigmond & Snaith, 1983). Mental wellbeing levels on the WEMWBS were at the low end of average results (40-59) (Tennant et al., 2007) and social resilience scores were considerably lower than the general population (80.7) and also lower than either psychiatric outpatients or those with generalised anxiety disorder (68 and 62.4 respectively) (Connor & Davidson, 2003).

5.3.6 Phase 2: Emotion results

Baseline levels revealed no significant differences between the drumming activity and the other activities in terms of emotion, except for self-reported tiredness ($F_{3,102}$=3.427, p=0.02) with participants reporting feeling significantly more tired prior to the listening condition compared to prior to drumming ($F_{1,34}$=6.910, p=0.013). Preliminary T tests showed that drumming led to significant changes in 11 of the 12 emotions assessed: decreases in fear ($t_{(36)}$=-3.111, p=.004), sadness ($t_{(36)}$=-4.216, p<.001), anger ($t_{(36)}$=-4.706, p<.001), tiredness ($t_{(36)}$=-2.624, p=.013), tension ($t_{(35)}$=-4.570, p<.001), anxiety ($t_{(36)}$=-4.913, p<.001) and stress ($t_{(36)}$=-4.809, p<.001) and increases in energy ($t_{(36)}$=3.094, p=.004), happiness ($t_{(36)}$=5.559, p<.001), relaxation ($t_{(36)}$=3.574, p=.001) and connectedness ($t_{(36)}$=3.708, p=.001). In this second phase, there were more significant responses to the control conditions. In the watching condition, seven emotions changed: decreases in fear ($t_{(35)}$=-2.529, p=.016), anger ($t_{(35)}$=-3.758, p=.001), anxiety ($t_{(35)}$=-2.878, p=.007), and stress ($t_{(36)}$=-3.669, p=.001), and increases in happiness ($t_{(35)}$=2.628, p=.013), relaxation

($t_{(36)}$=6.199, p<.001) and connectedness ($t_{(36)}$=3.708, p=.001). In the listening condition, there were changes in seven emotions: decreases in anxiety ($t_{(35)}$=-2.287, p=.028), confusion ($t_{(35)}$=-2.822, p=.008), anger ($t_{(34)}$=-2.259, p=.03), tiredness ($t_{(35)}$=-2.187, p=.036), stress ($t_{(35)}$=-3.242, p=.003) and tension ($t_{(35)}$=-2.090, p=.044) and increases in happiness ($t_{(35)}$=3.080, p=.004), relaxation ($t_{(35)}$=2.971, p=.005) and connectedness ($t_{(34)}$=2.505, p=.017). Finally, in the audio control condition there were changes in seven emotions: decreases in fear ($t_{(36)}$=-2.705, p=.01), anger ($t_{(36)}$=-2.543, p=.015), tension ($t_{(36)}$=-3.490, p=.001), anxiety ($t_{(36)}$=-3.598, p=.001) and stress ($t_{(36)}$=-4.122, p<.001) and increases in relaxation ($t_{(36)}$=3.389, p=.002) and connectedness ($t_{(36)}$=2.961, p=.005). When controlling for multiple comparisons at the strictest level, the drumming group still had significant differences in anger, happiness, sadness, stress and tension; the watching group had significant relaxation; and the audio control group had significant differences in stress.

As in phase 1, the majority of the changes in the control conditions related to alterations in emotions indicative of stress (tense, relaxed, anxious, stressed). However, there were some significant alterations too in emotions indicative of negative affect. There was no interaction evident between the order the control conditions were experienced in during the four weeks and these alterations in emotion or affect, suggesting this was not a habituation effect to the study as a whole.

Building on the exploratory results of phase 1, phase 2 revealed a significant overall difference in energy level across time ($F_{1,35}$=5.563, p=.024), between condition ($F_{3,105}$=2.829, p=.042) and a near-significant interaction between time and condition ($F_{3,105}$=2.279, p=0.084). Planned within-subject contrasts for condition showed that there were significantly higher energy levels in the drumming condition than either the listening condition ($F_{1,35}$=10.164, p=0.003) and the audio control condition ($F_{1,35}$=4.278, p=.046).

As building on the phase 1 results, there was a significant overall difference in happiness across time ($F_{1,34}$=29.284, p<.001) and the interaction between time and condition ($F_{3,102}$=4.385, p=.006), but not between condition. Planned within-subject contrasts of the time by condition interaction showed that drumming led to a significantly greater increase in happiness than the audio control activity ($F_{1,34}$=12.156, p=0.001) and the listening activity ($F_{1,34}$=7.175, p=0.011). However, listening did lead to some

improvements albeit not as large as the drumming condition**.** This suggests that music specifically was involved in the induction of happiness during this intervention, but the physical activity of drumming led to a greater induction.

Moving beyond the findings in phase 1, there was also a significant overall difference in anger across time ($F_{1,33}$=38.498, p<.001) and a near significant overall interaction of time by condition ($F_{3,99}$=2.651, p=0.053) but no significant difference between condition. Planned within-subject contrasts of the time by condition interaction revealed that drumming led to significantly greater reductions in anger compared to the audio control condition ($F_{1,33}$=7.271, p=0.011) and listening ($F_{1,33}$=4.762, p=0.036). However, in this study, both watching and listening did lead to some reductions albeit not as large as the drumming condition**.** This suggests that the physical activity of drumming was important in anger reduction, hinting at a possible therapeutic role of the physical component of drumming in reductions of negative emotion.

There was also a significant overall difference in tiredness across time ($F_{1,35}$=7.293, p=.011) and condition ($F_{3,105}$=6.263, p=.001), but not the time by condition interaction. Planned within-subject contrasts across condition showed that there were significantly lower tiredness levels in the drumming condition compared to either the listening condition ($F_{1,35}$=5.125, p=.03) and the audio control condition ($F_{1,35}$=16.748, p<.001). No significant changes across condition or time by condition interaction were found across other emotions.

When controlling for multiple comparisons at the strictest level the changes across time in happiness and anger held. Applying the planned mid-level correction, changes in tiredness between condition also held.

Table 25. Changes in emotion in response to group drumming and each of the three control conditions in phase 2

	Drumming				Watching				Listening				Audio			
	Baseline	Mean change[b] SD		p[a]	Baseline	Mean change SD		p[a]	Baseline	Mean change SD		p[a]	Baseline	Mean change SD		p[a]
Afraid	21.19	-7.05	13.79	**0.004**	18.58	-6.75	16.02	**0.016**	20.58	-3.83	12.77	0.08	20.43	-6.43	14.46	**0.01**
Angry	29.19	-16.78	21.70	**<.001**	25.86	-13.33	21.29	**0.001**	27.81	-7.74	20.27	**0.030**	21.11	-6.14	14.67	**0.015**
Anxious	40.70	-19.32	23.93	**<.001**	43.25	-14.64	30.52	**0.007**	44.94	-7.64	20.04	**0.028**	45.36	-16.22	27.05	**.001**
Confused	22.92	-3.49	14.09	0.141	22.75	-6.17	22.54	0.110	25.89	-8.39	17.84	**0.008**	21.19	-3.97	17.67	0.180
Connected	50.03	15.76	25.85	**.001**	53.95	8.19	21.04	**0.023**	53.17	7.63	18.02	**0.017**	49.97	10.32	21.21	**0.005**
Energetic	52.86	13.54	26.62	**0.004**	51.57	5.00	27.10	0.269	46.94	4.69	24.69	0.262	52.14	0.62	21.88	0.864
Happy	50.43	21.62	23.66	**<.001**	53.92	11.61	26.51	**0.013**	52.03	8.81	17.15	**0.004**	56.38	3.49	17.06	0.222
Relaxed	53.51	17.27	29.40	**0.001**	50.73	25.92	25.43	**<.001**	47.42	15.61	31.52	**0.005**	53.84	14.14	25.37	**0.002**
Sad	32.03	-11.76	16.96	**<.001**	29.81	-6.19	21.81	0.093	33.28	-6.22	26.54	0.168	28.03	-4.00	19.38	0.217
Stressed	44.24	-19.38	24.51	**<.001**	45.22	-19.38	32.13	**0.001**	49.53	-15.72	29.10	**0.003**	43.16	-15.14	22.34	**<0.001**
Tense	44.14	-20.06	26.33	**<.001**	37.46	-9.08	34.97	0.123	42.42	-8.86	25.44	**0.044**	40.08	-13.60	23.69	**0.001**
Tired	42.97	-11.41	26.44	**0.013**	43.05	-6.68	35.08	0.255	57.	-10.06	27.59	**0.036**	46.73	-2.46	20.97	0.480

Notes: SD: standard deviation

[a]P values shown. The most conservative Bonferroni adjustment is α<.001, the mid-level adjustment is α<.002 and the more lenient adjustment is α<.006.

[b]Mean change score across the intervention

5.3.7 Phase 2: Activity appraisal results

Appraisals of the activities showed significantly different results in terms of how stimulating ($F_{3,78}$=7.006, p<0.001), meaningful ($F_{3,78}$=4.231, p=0.015) and enjoyable ($F_{3,78}$=5.271, p=0.005) participants found them (see Figure 10).

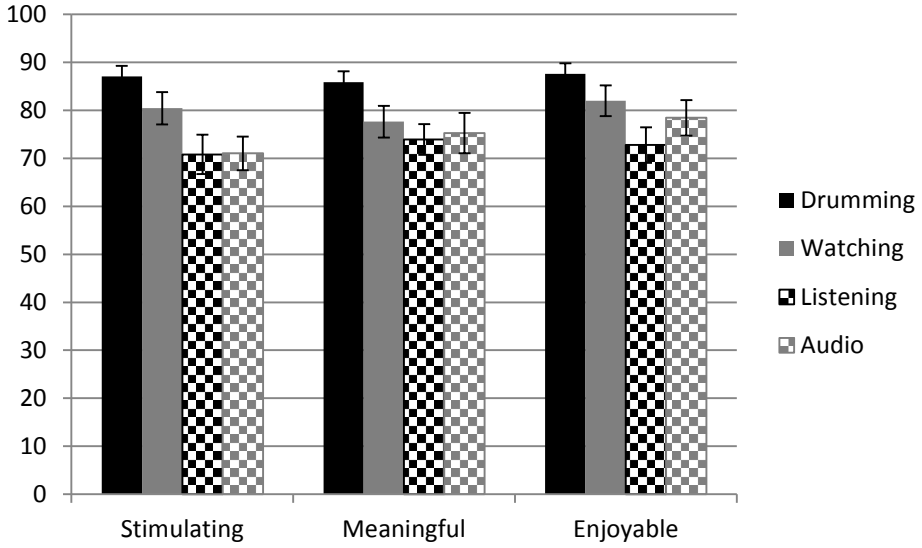


Fig 10. Mean appraisals (with standard error) of each condition for phase B

As in phase 1, planned within-subject contrasts demonstrated specifically that the drumming intervention was significantly more stimulating than the audio control condition ($F_{1,26}$=22.101, p<.001) and the listening condition ($F_{1,26}$=14.010, p=.001) but non-significantly more stimulating than the watching condition. And drumming was significantly more enjoyable than the listening condition ($F_{1,26}$=6.010, p=.021) and the audio control condition ($F_{1,26}$=16.178, p<.001), but again non-significantly more enjoyable than the watching condition, suggesting that the visual presence of drumming was an important variable. Drumming was also perceived to be more meaningful than either of the three control conditions (watching $F_{1,26}$=6.935, p=.014; listening $F_{1,26}$=5.927, p=.022; audio control $F_{1,26}$=25.655, p<.001). This data presents a slight departure from phase 1, in which the listening condition received stronger appraisals. When controlling for multiple comparisons at the strictest level changes in stimulation held, and when applying the most lenient level, bot the changes in meaning and enjoyment also held.

As in phase 1, activity appraisal was found to correlate significantly changes in emotions. When adjusting for age and gender, enjoyment was associated with 31% of the variance in happiness (B=1.033, SEM=.406, $t_{(27)}$=2.547, p=.018), perceived meaning for nearly 38% (B=1.198, SEM=.385, $t_{(27)}$=3.111, p=.005), and stimulation for 29% (B=.965, SEM=.410, $t_{(27)}$=2.351, p=.027). However, again sample sizes were small for regressions so this should be interpreted with caution.

5.3.8 Phase 2: Biological results

Assessments of the baseline levels revealed no significant differences between the drumming activity and the other activities. Changes in biomarkers are shown in Table 26. As in Phase 1, a number of samples fell below levels of detection which accounts for the small sample sizes in some of the groups, particularly for the biomarkers IL-2, IFN-γ and TNF-β. From before to after the drumming session, there was a significant increase in TNF-α ($t_{(28)}$=2.764, p=.01). In the watching condition, there was a similar increase in TNF-α ($t_{(30)}$=3.053, p=.005) which maintained its significance, alongside an increase in MCP-1 ($t_{(34)}$=2.598, p=.014) and a marginal decrease in IL-4 ($t_{(35)}$=-2.036, p=.05). In the listening condition, there was a decrease in IL-2 ($t_{(12)}$=-2.763, p=.017) and an increase in MCP-1 ($t_{(34)}$=2.573, p=.015). And in the audio control there were significant increases in TNF-α ($t_{(31)}$=2.226, p=.033) and MCP-1 ($t_{(33)}$=3.278, p=.002). When controlling for multiple comparisons at the strictest level none of the findings held.

To test hypothesis 2, that there were differences in biological measures between group drumming and the control activities, comparisons were made between the four conditions. No significant differences were found. However, as in Phase 1, retrospective power calculations showed that, due to the small sample sizes in each condition, there was not sufficient power to undertake comparisons between the four activities.

Table 26. Changes in biomarkers in response to group drumming and each of the three control conditions

	Drumming				Watching				Listening				Audio			
	Baseline[c]	Mean change[b] SD		p[a]	Baseline	Mean change SD		p[a]	Baseline	Mean change SD		p[a]	Baseline	Mean change SD		p[a]
IL-2	4.26 (13)	-0.59	0.45	.219	4.50 (19)	-0.69	0.35	.062	3.90 (13)	-0.66	0.24	**.017**	4.65 (13)	-0.82	0.56	.167
IL-4	1.87 (32)	-0.12	0.08	.163	1.86 (35)	-0.13	0.66	**.050**	1.87 (35)	-0.09	0.09	.324	1.92 (35)	-0.17	0.09	.073
IL-6	1.54 (33)	-0.01	0.08	.940	1.49 (33)	0.07	0.64	.261	1.61 (32)	0.06	0.09	.484	1.55 (33)	0.02	0.79	.780
IL-17	0.95 (27)	0.02	0.06	.725	0.98 (29)	-0.02	0.05	.719	0.97 (30)	-0.02	0.05	.678	0.97 (27)	0.02	0.49	.627
Cortisol	3.05 (34)	-0.07	0.11	.514	3.01 (37)	-0.04	1.33	.793	2.96 (36)	-0.12	0.13	.389	3.03 (36)	-0.21	0.13	.130
IFN-ɣ	1.12 (17)	-0.05	0.10	.650	1.15 (18)	-0.04	0.10	.700	1.13 (19)	-0.09	0.08	.275	1.12 (18)	-0.03	0.65	.622
TNF-α	1.22 (29)	0.27	0.10	**.010**	1.27 (31)	0.27	0.10	**.005**	1.32 (32)	0.20	0.10	.053	1.23 (32)	0.22	0.10	**.033**
TGF-β	2.15 (6)	1.42	0.71	.101	2.46 (11)	-0.13	0.47	.794	2.26 (12)	-0.01	0.43	.983	2.08 (11)	0.44	0.42	.314
MCP1	4.22 (33)	0.17	0.15	.269	4.14 (35)	0.34	0.13	**.014**	4.20 (35)	0.25	0.10	**.015**	4.14 (34)	0.50	0.15	**.002**

Notes: SD: standard deviation

[a]P values shown. The most conservative Bonferroni adjustment is α<.001, the mid-level adjustment is α<.002 and the more lenient adjustment is α<.006.

[b]Mean change score across the intervention

[c]The number of detectable samples per group is given in brackets.

When testing hypothesis 3, that emotional responses correlated with biological responses, as in phase 1, TNF-α emerged as being associated with emotions. A linear regression showed that TNF-α levels explained nearly 20% of variation in tension (B=-24.867, SEM=11.024, $t_{(26)}$=-2.256, p=.034). However, the sample size was smaller than usual for a regression analysis so results should be interpreted with caution. It was not possible to test responses in IFN-γ as too many samples fell above the upper limit of quantification. These results build on phase 1 by suggesting that biological responses are associated with some music-induced emotional responses, providing further support to hypothesis 3.

There was also preliminary evidence from this study that biological activity was associated with appraisal of the condition too. When adjusting for age and gender, cortisol explained 35% of the variance in how meaningful a participant rated drumming (B=7.799, SEM=2.962, $t_{(23)}$=2.633, p=.016) with increase in cortisol over the session found alongside higher levels of meaning associated with the activity. This builds on the finding in phase 1 that increases in cortisol was associated with decreases in sadness, suggesting that positive stimulation from music could lead to short-term increases in cortisol response alongside effects on emotion and appraisal, but again sample sizes are small.

5.4 Conclusion

This study lent partial support to the first hypothesis that group drumming leads to a greater change in self-reported emotion than control interventions. In Phase 1, there was preliminary evidence to support this as the drumming condition had more significant changes in self-reported emotion than the 3 control conditions. In Phase 2, this came through statistically in a more robust way through ANOVAs across time and between conditions, showing significantly greater changes in energy, happiness, anger and tiredness in the drumming condition.

The second hypothesis was that there would be differences in biological measures between the activities. Unfortunately, due to many samples falling below levels of detection, there was not enough power within the ANOVAs to detect changes. As discussed in section 4.4, this was perhaps due to the storage or transport of samples. Consequently, this second hypothesis could not really be tested.

The third hypothesis, that there is an interplay between emotion and biological response to group drumming, produced stronger results, with particular findings for TNF-α. The negative correlations between TNF-α and negative emotions is somewhat contradictory to previous psychobiological research which has tended to show increases in TNF-α in response to negative affect (Berk et al., 2001; Mittwoch-Jaffe, Shalit, Srendi, & Yehuda, 1995). As such it warrants further investigation. However, there is some precedent for reverse responses, with a previous study demonstrating that TNF-α was lower in high-anxiety exam students (Chandrashekara et al., 2007).

When controlling for multiple comparisons, several levels of strictness were applied. When looking at the more exploratory T tests, the total of 108 tests meant that the adjusted α was <.0005 which was a challenging threshold. Many of the findings did not hold when correcting, as anticipated given the large number of tests that were carried out. However, even when applying the strictest level of correction, there were significant changes in relaxation from drumming in phase 1 and changes in anger, happiness, sadness, stress and tension in phase 2. Interestingly, although the ANOVAs in phase 1 were underpowered, the ANOVAs from phase showed that differences in happiness and anger held, even at this very strict level of correction. When the mid-level correction was applied (which is what had been planned for in the study initially), there were also significant differences in tiredness. That these findings held even with these very strict corrections attests to the statistical strength of the associations. For biological data, no changes held at any level of correction, providing no support to the main hypothesis, although there were findings to support the third hypothesis, as discussed above. For connative meaning, at the planned mid-level, there were significant differences in the level of stimulation from the four activities in both phases. In phase 1, there also significant differences in enjoyment level, which was found at the more lenient level in phase 2, along with differences in perceived meaning in both phases. Stimulation actually held at the strictest level of correction in phase 2, attesting to the strength of the finding. This identifies that the activities did appear to modulate connative meaning of engagement. Regarding changes in psychological markers, at this same mid-level of correction, none of the ANOVAs were significant in phase 1, but in phase 2 there were significant differences in happiness, anger and tiredness; the first two of which actually held at the strictest level too, again attesting to the statistical strength of the finding. Regressions were reported here with the adjustments for age and gender made to the biological

marker given research showing that biological activity can alter with age (Graham, Christian, & Kiecolt-Glaser, 2006; K. Hirokawa, 1992). However, this is not to suggest that biological responses caused psychological responses, following the James-Lange theory of emotion (Cannon, 1927). Given the biological and psychological results were measured at the same time, there is no evidence in support of this. Rather, it is likely that these results are bidirectional and are parallel manifestations of an integrated psychobiological response (Solomon, 1987).

In addition to the three main hypotheses, the study also showed that group drumming led to greater levels of potency, arousal and valence. Drumming had significantly greater responses than the other three conditions, although there was evidence that watching and listening to drumming also led to increases, albeit smaller ones, across the three parameters. In both phases, physically drumming led to the highest levels of stimulation, meaning and enjoyment. This is not to say that performing music is always more enjoyable than listening to it; rather that within the context of a drumming intervention, the physical act of drumming makes a significant contribution to the overall appraisal of the activity, increasing the response in comparison to control activities where the physical component was missing. In phase 2, a tiered response response across the four activities was particularly evident, with the implication that each component (physical, visual and musical) added individually to the overall experience of participants. Interestingly, that there were associations between happiness levels and appraisal in phases 1 and 2. Previous research has suggested that intense emotions are linked to increased physiological arousal, which is supported by the correlations found here between happiness and stimulation (Rickard, 2004). In addition, there has been evidence to suggest that emotions are linked to how rewarding a participant finds a piece of music, which is again supported here by correlations between happiness and meaning (Salimpoor, Benovoy, Longo, Cooperstock, & Zatorre, 2009).

Although the two-phase design reinforced some of the main findings, specifically the effect of drumming on emotions, appraisal and specific biomarkers, there were also some discrepancies between emotions and biological response. Furthermore, this study also had some differences in results to drumming study 1. In study 1, increases were seen in cytokines IL-4, IFN-γ, MCP-1 and TNF-α across the first session. In this study, there were no significant changes found in Phase 1 and in Phase 2 there was an increase seen in TNF-α but this did not hold when controlling for multiple comparisons. There are a few possible explanations for this. For Phase

1, the sample size in this study was much smaller than study 1: 4-16 pairs of samples compared to 23-28. Consequently, there may not have been sufficient power to detect changes. For Phase 2, there were more samples: 13-34 pairs for the drumming condition. However, study 1 showed that with increased exposure to drumming, responses changed, with the 6th session of drumming showing increases in all the cytokines and a decrease in cortisol. For Phase 2, participants took part in drumming workshops on either weeks 1, 2, 3 or 4. For those who had drumming on weeks 2, 3 or 4 they had had prior exposure to a similar condition (such as watching drumming) which means they were not approaching drumming in the same new way that participants in study 1 were. This may have affected how people responded. However, it does not appear to provide a complete solution. Another possibility is that responses to group drumming are not as uniform as initial results might suggest. In 2005, a study examining the impact of music on the expression of 45 immune-response associated genes raised the question of whether there are clearly definable biological reactions to music or whether humans all have their own unique response (B. Bittman et al., 2005). Study 1 and the two phases presented here suggest that there are some broad responses to participation in music interventions, but there is also some between-subject variation, partly based on age and gender differences, but also relating to how participants appraise the condition, and consequently what biological and emotional effect it has on them. Further studies will be needed to ascertain these individual differences in more detail.

There are several limitations to this study. This study only assessed one intervention: group drumming. Consequently, it is not known whether these results extend to other music interventions. Although all participants were mental health service users, they were from a broad demographic: they were of different ages, ethnicities, and had differing levels of mental health. Further research is needed to ascertain whether there are different cultural or individual emotional and biological responses to group drumming. This study also only looked at the effects of single sessions of drumming and measured just acute responses. It is unknown how these responses would have differed over time or with repeat exposure to the intervention. We also assessed a number of variables and, although controlling for multiple comparisons where appropriate, these results should be taken in the exploratory way they are presented. Future studies will be needed to elucidate responses in more detail. The design of phase 1 was randomised although participants still expressed an interest in group drumming when they chose to participate. However, phase 2 involved only a subset of

this larger initial population and as such although there were no baseline differences in measured variables, the group was self-selecting so care should be taken in generalising results. Finally, aside from excluding participants with self-reported gum disease, we did not assess the oral health of participants, and this may have contributed to variations in response between participants (Slavish et al., 2015).

Overall, this study suggests the potential of group drumming to modulate emotions and provides preliminary evidence of the interconnectedness of psychological and biological processes in music-induced emotions.

6 PART II: MENTAL HEALTH AND CANCER STUDY

6.1 Introduction

Part I of this PhD involved the study of the effects of participatory music interventions on the psychobiology of mental health. Part II of this PhD (and planned post-doctoral work) aims to expand this and explore how participatory music interventions can interact with the psychobiology of mental health conditions for patients diagnosed with a chronic disease. Part II was funded by Tenovus in Wales: an organisation exploring the effects of psychosocial interventions on patients and relatives affected by cancer. The funding made available through Tenovus steered the focus of Part II onto cancer and also meant that the intervention being investigated turned to singing.

6.1.1 Biobehavioural influences on cancer

Over 14 million new cases of cancer are diagnosed worldwide each year; a figure estimated to rise by over 70% in the next two decades. Cancers accounted for 8.2 million deaths in 2012, and yet over 30% could be avoided by modifying behaviours and reducing environmental risk factors (Stewart & Wild, 2014).

The concept of psychological, social and behavioural factors having an influence on cancer has a long history. Indeed, as far back as Ancient Greece, writings of Galen discuss the links between 'melancholia' and cancer in women (McDonald et al., 2005). However, it has mainly been in the last thirty years that clinical trials have begun to be conducted in this field, with a burgeoning number of studies examining how psychosocial factors could act synergistically in combination with biological vulnerabilities such as genetic disposition and lifestyle to affect both the onset and progression of cancer (Sood, Lutgendorf, & Cole, 2007).

In particular, the negative effects of three key psychological factors have been explored in more detail:

Stress

Research around the effects of stress on cancer has been somewhat controversial. Some studies have proven no relationship at all (Bleiker, Hendriks, Otten, Verbeek, & Ploeg, 2008), suggesting that the effects of stress are not strong enough to have a marked influence on the disease. A few studies have demonstrated the links between stress and the induction of cancer development (Lillberg et al., 2003; Price et al., 2001), but meta-

analyses have yet to demonstrate a definitive link ((Chida, Hamer, Wardle, & Steptoe, 2008; Sood et al., 2007). However, when stress was more specifically defined such as the death of a child or spouse, it has been found to provide more consistent results (Sood et al., 2007), with implications it can play a role in certain circumstances as a risk factor for the onset of cancer.

More consistent evidence exists on the effect of stress on cancer progression (Antoni et al., 2006). For example, distress has been linked to lowered cell-mediated immunity such as NK cell and Th1 activity, subsequent impaired antigen presentation and increased stress hormones (Moreno-Smith, Lutgendorf, & Sood, 2010), with another study demonstrating that stress contributed to 51% of the variance in NK cell activity (Levy, Herberman, Lippman, & d'Angelo, 1987). Chronic stress can also lead to the elevation of noradrenaline and adrenaline while depleting dopamine levels, leading to a more conducive microenvironment for tumour growth (Moreno-Smith et al., 2010). And stress and negative affective states associated with stressors can trigger the release of inflammatory cytokines (Powell, Tarr, & Sheridan, 2013; Andrew Steptoe, Hamer, & Chida, 2007).

Depression

Another key psychological factor explored in relation to cancer has been depression, with Sood, Lutgendorf, & Cole (2007) identifying the sustained activation of negative affect as having a significant impact on progression. Their paper summarised some evidence that previous psychiatric illness can lead to an increase in cancer incidence, as well as one recent study showing that past or current psychiatric illness led to lower NK cell activity, weakening the body's immunosurveillance capabilities. But in general, data around depression and cancer initiation remains weak (Sood et al., 2007).

However, the problems associated with depression and cancer have been studied in much more detail with respect to patients with active disease. Major depression rates are approximately five times higher in cancer patients than the general population; a figure expected to increase by 2030 (Irwin, Olmstead, Ganz, & Haque, 2013). Depression risks are greatest in the first six months of diagnosis (Schag et al., 1993) and have a four-fold increase again two years after diagnosis (Polsky et al., 2005). Many cases go undiagnosed, and only 30-

35% of patients achieve remission (Irwin et al., 2013). Depression in cancer is thought to lead to an increased risk of death somewhere between 19% and 33% (Mykletun et al., 2007; Onitilo, Nietert, & Egede, 2006). In part, this is attributed to negative changes in lifestyle associated with depression: depressed patients are less likely to adhere to recommended cancer treatment, three times less likely to adhere to medication and twice as likely to need to use emergency and medical services, as well as more likely to engage in health-impairing behaviours such as smoking and alcohol (Ehlers et al., 2011; Stagno, Busby, Shapiro, & Kotz, 2008). In addition, this link between depression and cancer deaths may be linked with depression further increasing inflammation in patients (Dahl et al., 2014; Dowlati et al., 2010). Inflammatory responses are fundamental to cancer progression and are linked to 15-20% of cancer deaths worldwide (Mantovani, Allavena, Sica, & Balkwill, 2008). Heightened inflammation is a well-established immune profile in cancer (Rakoff-Nahoum, 2006) but is also exacerbated by certain cancer treatments with effects lasting long after treatment finishes. The effects of heightened inflammation can last long into survivorship, with potential subsequent effects on cancer recurrence or second malignancies (Irwin et al., 2013). Consequently, the pro-inflammatory effects of depression contribute to an already heavily-loaded inflammatory immune profile.

Loneliness

Finally, there is evidence as to the negative effects of loneliness on cancer. Loneliness or social isolation is categorised as a behavioural stressor which has been linked in some studies to the onset of cancer. For example, Price et al. (2001) found that if the effects of a threatening life stressor were combined with low social support they could lead to a nine-fold increase in breast cancer risk for women.

More research exists examining loneliness and cancer progression, with perceptions of problematic social support actually linked to an increased risk of mortality (Frick, Riedner, Fegg, Hauf, & Borasio, 2006). The physiological correlates of loneliness are also thought to continue into remission periods, with survivors reporting higher levels of pain and depression if they have low social support (Hughes et al., 2014). This link between loneliness, pain and depression is found in other studies, correlated with higher inflammatory levels, especially IL-6, suggesting an underlying immune dysregulation in people with low social support perhaps responsible (Hughes et al., 2014); (Costanzo et al., 2005). One particular study took this idea further, finding

that people with low social support also have greater anxiety and cortisol levels along with impaired transcription of glucocorticoid responses and increased activity of pro-inflammatory pathways (Lutgendorf, Sood, & Antoni, 2010). This attests to the powerful effect of social support on cancer patients.

6.1.2 Biobehavioural mechanisms

In light of this evidence linking negative psychosocial effects to physiological adaptation in cancer patients, there have been a number of studies that have explored whether improved cognitive, behavioural and social skills lead to better experience and outcomes for cancer patients (Antoni, 2013). In particular, (Lutgendorf, Costanzo, & Siegel, 2007) identified three key constructs important in achieving success through biobehavioural interventions:

Emotional expression

In contrast to suppression of negative emotions such as stress, hopelessness and denial which are linked with poorer survival and inflammation (Sood et al., 2007), emotional expression is linked with modulated inflammation such as lower IL-6 and TNF-RII (M. A. Hoyt, Stanton, Irwin, & Thomas, 2013) and higher lymphocytes at tumour sites (Temoshok et al., 1985).

Benefit finding

There is also evidence that the way that cancer is appraised may enhance adaptation and quality of life over time (Carver et al., 2005). An enhanced sense of meaning or purpose, heightened spirituality and greater appreciation for life are associated with greater lymphocyte proliferation response (McGregor et al., 2004), increased CD4+ and CD8+ and greater numbers of white blood cells (Sephton, Koopman, Schaal, Thoresen, & Spiegel, 2001).

Social support

In contrast to loneliness, improved social support has been linked to improved cellular immunity (Levy et al., 1987), better adaptation to cancer and improved longer term health outcomes (Nausheen, Gidron, Peveler, & Moss-Morris, 2009; Sood et al., 2007).

Notably, it is not just cancer patients for whom these factors are important. There is also increasing evidence as to the psychological stress of carers, including both informal carers and formal carers, including healthcare professionals (McManus, 2007). Studies have repeatedly reported how carers have practical unmet needs for service provision, health and community support and information as well as personal unmet needs, such as high stress and low social support themselves (Aoun, Kristjanson, Currow, & Hudson, 2005). The burden of caring has been linked with dysregulated immune function, including increased glucocorticoids and leukocyte suppression (Bauer et al., 2000; Bevans M & Sternberg EM, 2012). Consequently, biobehavioural factors are now recognised as important for the health of both cancer patients and carers.

6.1.3 Biobehavioural interventions

Over the past 50 years, over 300 studies have explored the combined psychological and biological value of psychosocial interventions from mindfulness to yoga to the arts for cancer patients, survivors and carers (Green McDonald, O'Connell, & Lutgendorf, 2013; Lutgendorf et al., 2007). Psychosocial interventions for all three populations have been found to reduce symptoms of depression and anxiety, increase social support networks, improve quality of life and raise perceptions of care (Lutgendorf et al., 2007). These positive states have, in turn, been linked with optimised immune responses including the lowering of inflammatory immune response, enhanced cellular function and other longer term health outcomes (Antoni et al., 2006; Sood et al., 2007). Such evidence suggests that psychosocial interventions could play an important role in optimising health in people affected by cancer, helping to put patients in the best position to receive treatment or maintain remission and supporting staff and relatives who care for someone with cancer.

Specifically, there has been a growing interest in the role of music as one such psychosocial intervention. Thirty randomised controlled trials were reviewed in a Cochrane Review on music and cancer (Bradt, Dileo, Grocke, & Magill, 2011) ranging from music therapy sessions to recorded music listening. Studies showed reductions in anxiety, improvements in mood and reductions in cardiovascular measures such as blood pressure. However, to date there has been little attention to the biological impacts of music interventions in cancer care. This is despite the growing evidence of the impact of music-making on neuroendocrine and immune responses in other patient populations (Fancourt et al., 2014).

However, there is evidence to suggest that music interventions could have a combined effect on the mental health and immune function of cancer patients and carers. First, both study 1 and study 2 have demonstrated that group music-making can affect mental health with parallel biological changes. Second, music interventions fulfil all three of the constructed outlined as important in biobehavioural research by Lutgendorf, Costanzo, & Siegel (2007): they have the potential to help participants express their emotions, enable them take up a new hobby and are inherently social. Third, an experimental paper published in 2002 showed that music played to rodents reduced the suppressive immune effects of stress associated with cancer, enhanced anti-tumour response and improved white blood cell function (Nunez et al., 2002).

6.1.4 Study introduction

Within service development, there are a growing number of organisations delivering singing programmes for people affected by cancer, including patients, carers and staff. One example of this is the work of Tenovus Cancer Care in Wales, whose choirs involve over 1,000 people affected by cancer singing every week. Research around these choirs has identified that long-term involvement across three and six months is associated with reduced levels of anxiety and depression and improved quality of life (Gale, Enright, Reagon, Lewis, & van Deursen, 2012). Singing has also been found to provide support and processing of grief for cancer patients and their families [26]. However, it remains unkown whether, parallel to psychosocial benefits, singing could have effects on immune response.

Consequently, a study was carried out in order to test whether group singing can lead to psychological and biological modulation in people affected by cancer. The study had two main aims: (i) to compare changes across time in two separate populations: cancer carers and cancer patients; (ii) to assess whether responses from the two groups differed from one another statistically in order to explore whether singing was of particular value for either carers or patients. Due to the different physical and emotional demands faced by current cancer carers and bereaved carers, they were split into two groups for the purposes of this study. As this was the first study looking at music-induced immune responses in this population, we focused on the effects of a single session of group singing on a range of biomarkers from the neuroendocrine and immune systems.

6.2 Methods

6.2.1 Design and participants

This was a multi-centre single-arm study comparing responses between three participant groups. In order to make sure that findings were not just specific to a single choir, five Tenovus Cancer choirs were approached via convenience sampling from a total of 18 choirs across Wales. A total of 193 participants consented to take part in the study (see Figure 11: current carers of someone with cancer (n=72), bereaved carers (n=66), cancer patients (n=55). Participants classed as cancer carers had to be either current carers for someone with cancer or a bereaved carer. Participants classed as cancer patients had to have a current diagnosis of cancer or be in remission. For both groups, participants had to have previously attended at least one choir session and were excluded if they were under 18 years of age, if they were currently registered on another clinical trial, if they had a diagnosis of mouth cancer as this would affect saliva samples, if they were pregnant, if they were currently undergoing any active cancer treatment including chemotherapy or radiotherapy, or if they were taking oral immunosuppressive drugs. The study protocol was approved by the Conservatoires UK Research Ethics Committee and all participants gave written informed consent prior to the study.

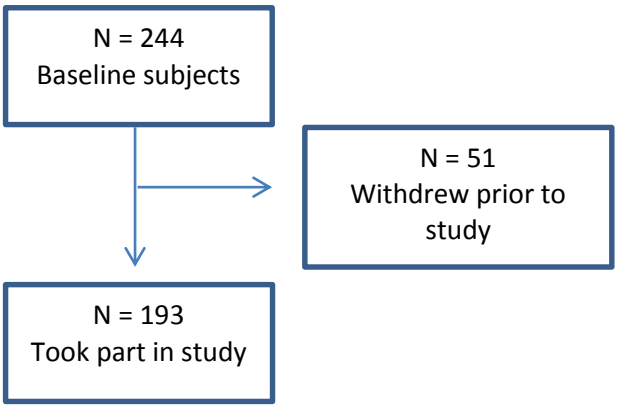


Fig 11. Recruitment of participants for study 4

6.2.2 Procedure

Participants took part in a single 70-minute choir rehearsal between 7pm and 8.15pm led by a trained Tenovus choir leader. Sessions consisted of warm-up exercises, learning new songs as a group and singing songs already in the singers' repertoire. We hypothesised that singing would lead to an increase in positive affect and a decrease in negative affect, alongside a decrease in neuroendocrine levels as measured with cortisol, an increase in immune activity and increases in oxytocin and beta-endorphin (PhD hypothesis 1). Furthermore,

we hypothesised interactions between these psychological and biological measures (PhD hypothesis 6). To test this, the week preceding the rehearsal, participants were asked to fill in a pack of demographic and psychological scales. Immediately before and after the rehearsal, participants gave a saliva sample and filled in a set of visual analogue scales (VAS).

6.2.3 Psychological measures

Participants' socio-demographic and health characteristics were obtained at baseline by means of a set of self-administered questionnaires including the Hospital Anxiety and Depression Scale (HADS), the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS), and the Connor-Davidson Resilience Scale (CD-RISC). These measures were described in section 3.2.3.

In addition, two types of visual analogue scales (VAS) were used. Visual Analogue Mood Scales (VAMS) and a trio of visual analogue stress scales as well as a final visual analogue scale assessed social connectedness. These measures were described in detail in section 3.2.3.

6.2.4 Biological measures

Saliva analyses were carried out as in previous studies using saliva multiplex assays. The samples were analysed for the same biomarkers as studies 1, 2 and 3: cortisol, IL-2, IL-4, IL-6, IL-17, IFN-ɣ, TNF-α and MCP-1. However, several more biomarkers were added to expand this selection. We included two soluble receptors, soluble interleukin 2 receptor alpha (sIL2Rα) and soluble tumour necrosis factor receptor 1 (sTNFr1) which have both been found to increase in patients with depression (Allen-Mersh, Glover, Fordy, Henderson, & Davies, 1998; Grassi-Oliveira et al., 2009). We also included the stem-cell differentiator growth factor granulocyte macrophage colony stimulating factor (GM-CSF) as indicators of cellular involvement. GM-CSF was selected as it plays a role in stem cell differentiation, which is particularly important in cancer patients (Francisco-Cruz et al., 2014).The neuropeptides oxytocin and β-endorphin were selected due to their specific involvement in relevant psychological processes. Specifically, oxytocin has been implicated in social bonding and β-endorphin in feelings of elation (Bartz, Zaki, Bolger, & Ochsner, 2011; Øktedalen, Solberg, Haugen, & Opstad, 2001; Olff et al., 2013).In addition None of these six additional biomarkers has been explored in relation to making music before. An overview of the role of each biomarker can be found in Appendix 1.

6.2.5 Statistical analyses

Sample size calculations using an alpha of 0.05, power of 0.8 and an effect size of 0.25 suggested an overall total of 34 participants would be required per group analysed. However, due to the large number of measurements being taken, this was significantly increased, especially for the cancer carers in order to allow for more statistical tests to be undertaken.

A one-way analysis of variance (ANOVA) was used to test for differences in baseline demographic data between choirs and between patients versus carers. Repeated measures ANOVAs were used for psychological and biological data to test across time (pre- vs post-singing) and between group (carers vs bereaved carers vs patients). The distribution of all biomarkers was positively skewed, and so the data were logarithmically transformed. As there were 12 mood states and 13 biomarkers assessed (a total of 25 markers), the significant p value for pre-post comparisons using Bonferroni's adjustment was $\alpha < .002$. Due to the larger sample size in this study, this strictest level was used across the study with no more lenient levels applied.

In addition to measuring mood through the eight components of the visual analogue mood scale, negatively-scored mood ratings were reverse scored and Cronbach's alpha was calculated using all eight mood states to reflect a single aggregate measure of mood with higher levels indicating more positive mood. Similarly, the three components of the visual analogue stress scale were reverse scored and combined onto a single aggregate measure of mood, with higher levels indicating higher stress.

Correlations between psychological variables and between biomarkers respectively were made using Pearson's product moment correlation coefficient. For interactions between psychological and biological data, Pearson's product moment correlation coefficients were run and, where significant, regression models were developed with adjustments made for age and sex. Some biomarkers fell below the levels of detection during analysis which accounts for the adjusted degrees of freedom.

6.3 Results

6.3.1 Descriptive statistics

Table 27. Overall demographic and psychological characteristics of cancer carers and patients

	CARERS (n=72)	BEREAVED CARERS (n=66)	PATIENTS (n=55)	$F_{df,df}$	p
Age (SD)	56.86 (13.64)	59.69 (11.46)	60.81 (8.99)	$1.91_{2,186}$	.151
Sex (% women)	80.6%	81.8%	80.0%		
Rehearsals attended (SD)	44 (23)	46 (26)	44 (23)	$0.11_{2,190}$	.892
Psychological profile (SD)					
HADSA	6.82 (4.08)	7.65 (3.71)	7.06 (4.27)	$0.77_{2,192}$	.464
HADSD	3.25 (2.87)	3.74 (3.13)	4.22 (3.96)	$1.35_{2,192}$	.261
CDRISC	47.89 (15.39)	49.09 (12.34)	48.27 (14.74)	$0.38_{2,191}$	.686
WEMWBS	64.47 (24.55)	67.46 (19.65)	66.82 (17.87)	$0.13_{2,192}$	.881
Medication type (%)					
None	37.5%	33.9%	60%		
Hormonal	6.9%	12.8%	29.1%		
Analgesic	5.6%	7.6%	5.5%		
Antidepressant	4.2%	12.2%	3.6%		
Antibody			1.8%		
Cholesterol	4.2%	1.5%	0		
Statins	4.2%	12.2%	1.8%		
Blood pressure	15.3%	25.8%	3.6%		
Cancer status (%)					
Current cancer			25%		
In remission			75%		
Cancer type (%)					
Breast			43.9%		
Skin			17.1%		
Gynaecological			14.6%		
Prostate			7.3%		
Thyroid			4.9%		
Lymphoma			4.9%		
Leukaemia			2.4%		
Head/neck			2.4%		
Bone			2.4%		

One hundred and thirty-eight carers and fifty-five patients took part in the study, the majority white females (Table 27). Participants across both groups were on average not symptomatic of having depression or anxiety and had average levels of wellbeing (Tennant et al., 2007; Zigmond & Snaith, 1983). However, their social resilience scores were considerably lower than the general population (cf. 80.7) (Connor & Davidson, 2003). Oneway analyses of variance revealed there were no significant differences in demographic data between the five choirs nor between the carers and the patients.

6.3.2 Psychological results

Across time

There were no significant differences in mood at baseline between the three groups. Across a single choir session, there were significant effects of time across all twelve moods assessed, with increases in positive affect and decreases in negative affect (all $p<.001$) (Table 27). These were all found below the Bonferroni correction threshold of $\alpha<.002$. Exploratory analyses showed that these results were found consistently for all 5 choirs with no statistical difference in response.

Responses to all eight moods were correlated, as were responses to the three stress items, so for both, negatively scored constructs were reverse scored and aggregate mood and stress scales were constructed. For the aggregate scale for mood, Cronbach's alpha was 0.83 for 'pre' measurements and 0.82 for 'post' measurements and for the aggregate scale for stress, Cronbach's alpha was 0.77 for both 'pre' and 'post' measurements indicating that the component ratings were reliably interrelated. Aggregate mood was found to improve across the choir session ($p<.001$) and aggregate stress was found to decrease ($p<.001$).

Mood was particularly found to increase for those who had lower mental wellbeing, with significant positive correlations between changes in mood and baseline anxiety levels ($r=.261$, $p<.001$) and depression levels ($r=.314$, $p<.001$), and significant negative correlations between changes in mood and baseline levels of both wellbeing ($r=-.222$, $p=.002$) and social resilience ($r=-.180$, $p=.013$). Furthermore, there was a significant negative correlation between baseline mood and change in mood score across the intervention ($r=-.680$, $p<.001$). Similarly, stress was found to decreases particularly for those with higher anxiety and depression levels ($r=-.273$, $p<.001$ and $r=-.267$, $p<.001$). However, there was less of an association shown with positive measures of wellbeing, with no significant correlation with social resilience and only a very small correlation with wellbeing ($r=.154$, $p=.034$). As with mood, participants with higher levels of stress at baseline experienced the greatest changes during singing ($r=-.789$, $p<.001$).

Between group

There were no significant differences between the three groups in individual or aggregate measures of mood, stress or connectedness, indicating a general consistency of effect (Table 28).

Table 28: Mood levels of cancer carers and cancer patients before and after a choir session

	CARERS		BEREAVED CARERS		PATIENTS		Time			Time*group		
	Mean (SEM)		Mean (SEM)		Mean (SEM)							
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**	$F_{df,df}$	p	Effect size (f)	$F_{df,df}$	p	Effect size (f)
Mood scales												
Afraid	13.5 (1.8)	6.5 (1.1)	11.3 (1.9)	6.3 (1.2)	10.2 (2.1)	7.8 (1.3)	$34.96_{1,187}$	**<.001**	0.41	$2.41_{2,187}$	.093	0.16
Angry	12.5 (1.8)	6.4 (1.5)	13.1 (1.9)	8.5 (1.6)	12.5 (2.1)	9.7 (1.7)	$19.15_{1,186}$	**<.001**	0.32	$0.86_{2,186}$	.423	0.10
Confused	12.0 (1.9)	7.5 (1.3)	9.6 (2.0)	7.0 (1.3)	16.7 (2.2)	8.9 (1.5)	$23.82_{1,185}$	**<.001**	0.36	$2.05_{2,185}$	.132	0.15
Energetic	49.6 (3.2)	77.0 (2.7)	49.5 (3.2)	70.6 (2.8)	47.5 (3.7)	72.6 (3.2)	$140.44_{1,186}$	**<.001**	0.87	$0.88_{2,186}$	.416	0.10
Happy	70.9 (2.7)	84.5 (1.9)	65.0 (2.8)	81.0 (1.9)	63.4 (3.1)	83.6 (2.2)	$112.01_{1,187}$	**<.001**	0.77	$1.44_{2,187}$	.239	0.12
Sad	16.1 (2.3)	7.1 (1.5)	20.5 (2.4)	10.5 (1.5)	14.9 (2.6)	9.4 (1.7)	$40.78_{1,184}$	**<.001**	0.47	$1.02_{2,184}$	.362	0.11
Tense	22.6 (2.7)	11.8 (1.9)	25.7 (2.8)	13.7 (1.9)	27.3 (3.2)	14.0 (2.2)	$55.58_{1,187}$	**<.001**	0.54	$0.19_{2,187}$	.831	0.04
Tired	37.7 (3.0)	19.9 (2.8)	43.6 (3.0)	25.7 (2.8)	41.4 (3.4)	28.8 (3.2)	$64.92_{1,185}$	**<.001**	0.59	$0.71_{2,185}$	.492	0.09
Stress scales												
Anxious	21.3 (3.0)	9.3 (1.8)	26.5 (3.1)	12.1 (1.8)	30.1 (3.5)	13.1 (2.1)	$68.40_{1,187}$	**<.001**	0.61	$0.65_{2,187}$	.522	0.08
Relaxed	66.9 (3.0)	85.3 (1.9)	63.5 (3.1)	81.4 (2.0)	65.8 (3.4)	82.0 (2.2)	$110.31_{1,187}$	**<.001**	0.77	$0.15_{2,187}$	.860	0.04
Stressed	23.8 (3.1)	11.1 (1.9)	32.5 (3.2)	14.3 (1.9)	29.9 (3.6)	11.8 (2.1)	$88.02_{1,187}$	**<.001**	0.69	$1.15_{2,187}$	.320	0.11
Connectedness												
Connected	71.9 (3.0)	89.9 (2.1)	66.4 (3.2)	80.4 (2.2)	72.2 (3.5)	85.5 (2.5)	$107.72_{1,186}$	**<.001**	0.76	$1.10_{2,186}$	.337	0.11
Aggregate scales												
Mood	75.6 (14.2)	87.8 (10.4)	73.8 (14.7)	85.0 (10.2)	73.5 (13.2)	84.8 (11.4)	$162.10_{1,187}$	**<.001**	0.93	$0.13_{2,187}$	.880	0.03
Stress	26.1 (19.2)	11.7 (11.7)	31.8 (22.1)	15.0 (14.3)	31.4 (21.6)	14.3 (12.9)	$144.83_{1,187}$	**<.001**	0.88	$0.45_{2,187}$	.640	0.07

6.3.3 Biological results

Across time

There were no significant differences in biological response at baseline between the three groups. Across a single choir session, there were significant effects of time for twelve of the thirteen biomarkers assessed; ten of which held when controlling for multiple comparisons with $\alpha < .002$ (Table 29). Exploratory analyses showed that these results were found across all 5 choirs with no statistical difference in response.

Overall, across all three groups, the results showed a significant decrease in cortisol and neuropeptide levels accompanied by an acute increase in cytokine and receptor activity (GM-CSF, IL17, IL2, IL4, TNFα, sIL-2rα and sTNFr1) suggestive of a general activation of the cytokine network. However, IFNγ and IL6 did not fall below the adjusted significance value of p<.002, and there was also no significant change over time for MCP1.

Change in cortisol had a medium-sized negative correlation with changes in IL2 (r=-.485, p<.001), TNF-α (r=-.326, p<.001), sIL2rα (r=-.339, p<.001) and IL4 (r=-.458, p<.001) and a small-sized negative correlation with changes in sTNFr1 (r=-.276, p=.001), IFN-γ (r=-.215, p=.007), IL17 (r=-.281, p=.001) and GM-CSF (r=-.227, p=.009). There were no correlations between change in cortisol and changes in IL-6 or MCP-1.

In addition to a decrease in cortisol (p<.001), there was also a decrease in both beta-endorphin (p<.001) and oxytocin (p<.001). Both neuropeptides had medium to large correlations with all cytokines ($-3.67 < r < -.653$, all p<.001) except MCP-1 for which there was a small correlation with beta-endorphin (r=-.286, p=.004) but no correlation with oxytocin. Both oxytocin and beta-endorphin were also positively correlated with cortisol (r=.427, p<.001 and r=.384, p<.001 respectively). Indeed, change in cortisol accounted for 20% of the variance in oxytocin levels (B=0.965, SEM=.208, $t_{(93)}$=4.641, p<.0001) and 17% of the variance in beta-endorphin levels (B=0.589, SEM=0.129, $t_{(120)}$=4.562, p<.001) when adjusted for age and sex. Oxytocin and beta-endorphin were also both highly correlated with one-another (r=.804, P<.001).

Between group

Changes in a number of markers were consistent across the three groups. However, there were significant differences in response in three biomarkers: IL17, MCP1 and sTNFr1. Pairwise comparisons showed that there were significant increases in sTNFr1 in carers (p=.003) and bereaved carers (p<.001), but not in patients

(p=.182). Pairwise comparisons also showed that bereaved carers only showed increases in MCP1 (p=.022) but carers did not show a significant increase (p=.567) and patients actually showed a decrease, although this did not reach significance (p=.166). Bereaved carers also showed the greatest IL17 responses with an increase across singing (p<.001). An increase was also seen for patients (p=.01) but not significantly for non-bereaved carers (p=.06).

6.3.4 Psychobiological interactions

3.4.1 Across time

Change in the aggregate mood score was negatively correlated with post-intervention measures of IL-6, IL-17 and MCP-1 but none of the other cytokines. As all three biomarkers are often classed as pro-inflammatory markers, this demonstrates that improvements in mood were associated with lower levels of pro-inflammatory response but had no effect on anti-inflammatory response. In particular, a regression model adjusted for age and sex showed that mood explained 10% of the variance in MCP-1 (B=-2.215, SEM=1.002, $t_{(134)}$=-2.211, p=.029) and once age and sex had been adjusted for, had a marginal effect on both IL-6 (R^2=.103, B=-1.797, SEM=1.035, $t_{(181)}$=-1.737, p=.084) and IL-17 (R^2=.114, B=-0.958, SEM=0.554, $t_{(173)}$=-1.728, p=.086). There were no associations between the aggregate stress score and pro-inflammatory levels or other biomarkers.

In addition, self-reported connectedness had a small positive correlation with beta-endorphin, accounting for 6% of the variation(B=2.991, SEM=1.107, $t_{(134)}$=2.703, p=.008) and a near-significant correlation with oxytocin, accounting for 4% of the variation (B=1.422, SEM=0.773, $t_{(103)}$=1.840, p=.069). No correlations were found between beta-endorphin, oxytocin and aggregate mood or stress scores.

Table 29. Biomarker concentration levels before and after a choir session

	CARERS		BEREAVED CARERS		PATIENTS		Time			Time*group		
	Mean (SEM) pg/ml		Mean (SEM) pg/ml		Mean (SEM) pg/ml							
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**	$F_{df,df}$	p	Effect size (f)	$F_{df,df}$	p	Effect size (f)
Cytokines												
GM-CSF	2.55 (0.12)	2.88 (0.12)	2.83 (0.13)	3.12 (0.12)	2.77 (0.14)	3.00 (0.13)	$32.14_{1,161}$	**<.001**	0.45	$0.38_{2,161}$	.686	0.07
IFNg	4.23 (0.16)	4.27 (0.14)	4.05 (0.17)	4.45 (0.15)	4.39 (0.19)	4.53 (0.17)	$4.82_{1,184}$	**.029**	0.16	$1.59_{2,184}$	.208	0.13
IL-17	4.06 (0.19)	4.40 (0.19)	3.64 (0.21)	4.66 (0.21)	3.86 (0.22)	4.40 (0.22)	$31.54_{1,171}$	**<.001**	0.43	$3.33_{2,171}$	**.038**	0.19
IL-2	3.32 (0.11)	3.67 (0.10)	3.48 (0.12)	3.78 (0.11)	3.39 (0.13)	3.69 (0.12)	$41.16_{1,178}$	**<.001**	0.48	$0.10_{2,178}$	.903	0.03
IL-4	2.48 (0.08)	2.68 (0.08)	2.51 (0.09)	2.77 (0.09)	2.60 (0.09)	2.79 (0.09)	$33.31_{1,175}$	**<.001**	0.44	$0.39_{2,175}$	.677	0.06
IL-6	2.62 (0.11)	2.78 (0.97)	2.53 (0.12)	2.70 (0.10)	2.75 (0.13)	2.79 (0.11)	$5.33_{1,185}$	**.022**	0.17	$0.53_{2,185}$	.590	0.08
MCP-1	6.19 (0.12)	6.27 (0.14)	5.85 (0.12)	6.19 (0.14)	6.09 (0.14)	5.85 (0.16)	$0.46_{1,128}$	.501	0.06	$3.28_{2,128}$	**.041**	0.23
TNF-a	2.84 (0.13)	3.09 (0.13)	2.70 (0.14)	3.12 (0.14)	2.63 (0.16)	3.00 (0.15)	$32.95_{1,185}$	**<.001**	0.42	$0.81_{2,185}$	.445	0.10
Receptors												
sIL-2ra	4.27 (0.14)	4.47 (0.13)	4.24 (0.15)	4.68 (0.14)	4.41 (0.16)	4.71 (0.15)	$21.10_{1,152}$	**<.001**	0.37	$1.09_{2,152}$	.340	0.12
sTNFr1	4.62 (0.14)	4.95 (0.14)	4.69 (0.15)	5.26 (0.15)	4.80 (0.16)	4.97 (0.16)	$28.71_{1,182}$	**<.001**	0.40	$3.13_{2,182}$	**.046**	0.18
Neuropeptides												
β-endorphin	4.79 (0.23)	4.20 (0.24)	4.57 (0.24)	3.79 (0.24)	4.55 (0.27)	4.11 (0.28)	$23.36_{1,135}$	**<.001**	0.42	$0.58_{2,135}$	.561	0.10
Oxytocin	5.14 (0.32)	3.74 (0.31)	5.15 (0.35)	3.88 (0.35)	4.45 (0.36)	3.62 (0.35)	$33.19_{1,103}$	**<.001**	0.57	$0.72_{2,103}$	.490	0.12
Glucocorticoids[a]												
Cortisol	2.73 (0.14)	2.18 (0.13)	2.96 (0.16)	2.45 (0.15)	2.91 (0.17)	2.47 (0.15)	$48.46_{1,156}$	**<.001**	0.56	$0.19_{2,156}$	.831	0.04

6.5 Discussion

The primary aim of this study was to explore whether group singing was associated with modulations in mood and neuroendocrine, neuropeptide and immune responses in three different groups affected by cancer who were regularly involved in choirs: carers, bereaved carers and patients. Our results demonstrated that a single hour of singing was associated with increases in positive affect, decreases in negative affect, a decrease in cortisol, beta-endorphin and oxytocin and a general activation of the cytokine network. The secondary aim was to explore differences in response between these four groups. Despite no baseline differences in response between the four groups, there were significant differences in response in three biomarkers: MCP1, IL17 and sTNFr1.

The main finding from this study is that singing was associated with a decrease in cortisol and increase in cytokine activity, found generally consistently across all five choirs and among all four groups. Previous studies involving singing have demonstrated that singing can modulate cortisol levels (Fancourt, Aufegger, & Williamon, 2015; Gunter Kreutz, 2014). However, this is the first study to demonstrate that singing is associated with modulation of cytokines, receptors and neuropeptides involved in immune response. These findings of a parallel decrease in cortisol and increase in cytokine activity in response to a short music intervention replicate those of a previous study involving making music in which mental health service users and carers involved in group drumming sessions had increases in IL2, IL4, IFNɣ and TNFα alongside decreases in cortisol, as in this study (Fancourt et al., 2016). Furthermore, the same cortisol-cytokine negative relationship has been found in response to other psychosocial interventions in oncology (Antoni et al., 2006; Sood et al., 2007). One possible explanation for this response is that the reduction in cortisol following singing reduced glucocorticoid suppression of the immune system, leading to general activation of the cytokine network and increased immune activity (Petrovsky, McNair, & Harrison, 1998). Although, despite the correlations between cortisol and cytokines shown here, it is not possible to establish the direction of causality between the two.

Following on from this, there was also a pattern of a slightly weaker pro-inflammatory response compared with anti-inflammatory response among both carers and patients. There were no significant changes across time in the pro-inflammatory marker MCP-1, and similarly levels of IL-6 and IFN-γ reached significance using a p value of $p<.05$ but did not reach the adjusted significance value of $p<.002$. Furthermore, there was evidence that greater improvements in mood as a result of singing was associated with lower pro-inflammatory response. Interestingly, this appeared to be independent of stress levels. High levels of inflammation are associated with

many mental health conditions including depression (Dahl et al., 2014; Dowlati et al., 2010). It is instructive to note that, among both patients and carers, those with the lowest levels of mental wellbeing and highest levels of depression experienced the greatest short-term improvement in mood across the singing session, and that these larger mood changes were associated with lower levels of inflammation. A hypothesis to be tested further is whether singing on a regular basis leads to larger and more sustainable improvements in mood and whether this affects inflammatory response.

Another finding was that singing was associated decreases in oxytocin and beta-endorphin. This is contrary to some previous research: two previous studies found that oxytocin increased in response to music (Gunter Kreutz, 2014; U. Nilsson, 2009), although Kreutz's study notably did not find decreases for cortisol, while Nilsson's was in relation to listening to music and not singing. Similarly, the only previous study with beta-endorphin in response to listening to music found a reduction (McKinney et al., 1997). Oxytocin has been linked with social bonding and attachment, with higher oxytocin levels found, for example, in mothers and fathers in association with their social engagement with their children (Feldman, Gordon, & Zagoory-Sharon, 2011), and beta-endorphin is associated with feelings of euphoria (Boecker et al., 2008). However, both have also been found to be involved in stress regulation, with increased levels in response to a wide variety of stressful stimuli, serving to dampen blood pressure, heart rate and noradrenaline levels (Dubois et al., 1981, 1981; Olff et al., 2013). Indeed, there have even been suggestions of beta-endorphin being regulated alongside the stress hormone adrenocorticotropin in stress response by the pituitary gland (Guillemin et al., 1977). Given the correlations found between cortisol and both oxytocin and beta-endorphin and their correlations with one another, and the negative correlations between the neuropeptides and cytokines which mirrored the relationship between cortisol and the cytokines, it seems likely that the decrease found here was as part of a generalised down-regulation of stress response which may have over-ridden any social bonding or happiness-associated increase. Nevertheless, the positive associations found between changes in connectedness and beta-endorphin and near-significant associations with oxytocin may point to two contradictory processes at play.

In addition, this study examined differences in psychological and biological response between the three groups and as such whether singing is particularly effective for one group or equally beneficial for all. There were no significant differences in any of the psychological measures, suggesting that singing is similarly received by carers and patients. However, despite broadly similar responses in biomarkers, there were some discrepancies.

Patients exhibited no significant changes in sTNFr1 response, whereas both carers and bereaved carers showed significant increases. TNF-α and its soluble receptor sTNFr1 have been implicated in cancer physiology as both promotors and inhibits of tumour progression. Some studies have found associations between heightened levels and increased risk of some cancers (Dossus et al., 2011) as well as evidence that TNF-α is involved in tumorigenesis including cellular transformation, angiogenesis and metastasis (Sethi, Sung, & Aggarwal, 2008). However, TNF-α can also induce cancer cell death (X. Wang & Lin, 2008). Patients also showed opposite MCP1 responses to carers. MCP1 is a chemokine that recruits leukocytes including monocytes, dendritic cells and memory T cells to sites of inflammation (Carr, Roth, Luther, Rose, & Springer, 1994), but can also be produced by cancer cells themselves and alter tumour behaviour (Negus et al., 1995).The discrepancies in sTNFr1 and MCP1 activity in patients in response to singing, could be indicative that, although there may be broadly similar psychobiological pathways in response to singing, these responses are modulated by the specific immune profile of participants. However, the extent of this and the implications remain to be explored further. In addition, only bereaved carers showed significant responses in IL17 or MCP1, with no significant changes found for either carers or patients. Bereaved carers exhibited no baseline differences in mental health or either baseline levels or change scores in mood or stress compared to current carers or patients, suggesting that this was not a difference in psychological processing. Instead it may be that current carers and patients had blunted IL17 and MCP1 responses. However, given this was a preliminary study, it would be premature to draw any firm conclusions from these findings, and they deserve to be studied more.

There were several limitations to the study. The main limitation is that the study was a preliminary uncontrolled study, and it is therefore possible that some of these psychological and biological results found would have occurred in the absence of singing, if participants had simply rested for 70 minutes. However, there is evidence that cytokines do not routinely change across an hour in the absence of an intervention [43]–[45]. Furthermore, participants' stress levels were relatively low at the start of the session (23-33 on the visual analogue scale) suggesting that the findings were not wholly due to participants feeling acute stress at the start of the session that merely abated over the following hour. Nevertheless, a future controlled study is encouraged on the basis of these preliminary findings to explore these issues in more depth, and also explore which features of singing are most important (whether the social engagement of being in a choir, or the physical exercise of standing and singing for 70 minutes or the music itself). Second, we examined only the effects of a single session of singing.

It remains unknown whether repeated singing sessions could impact on immune function and specifically if the results noted here could be maintained over time. Third, the study focused on participants who were current members of choirs. The ethos of the choirs was that no prior experience was necessary, so many participants had no singing experience prior to enrollment in the choirs.But it was nevertheless a self-selecting sample. It remains unknown whether singing could be of benefit for people who would not normally opt to be involved in a choir. Finally, cancer patients involved in the study had varying types of cancer and were at varying stages of treatment. This was a short intervention and confounding factors such as immune-affecting medication were removed to allow data to be analysed. However, it would be revealing to explore in more detail the effects of singing with defined patient groups and at targeted timepoints in cancer progression in order to confirm whether singing can have biologically meaningful effects.

In conclusion, this study demonstrates associations between singing and reduced negative and increased positive affect, reduced cortisol, oxytocin and beta-endorphin and increased levels of cytokines. This is the first study to demonstrate the wide-spread immune effects of singing, in particular its effects on cytokines. Notably, the choice of biomarkers within this study included several that play important roles in cancer, including TNFα and the stem cell differentiator GM-CSF. Within the context of this preliminary study involving a single session of group singing, it is not possible to ascertain the implications of these changes, as they appear to occur as part of an acute non-specific cytokine activation. However, it would be of interest to ascertain whether such changes could be sustained with repeated exposure to the intervention over a longer time-span and with more specific patient groups. Such research could identify whether the psychosocial benefits of a communal activity such as group singing could lead to enhanced immune function in patients and carers affected by cancer.

7 CONCLUSION

7.1 Aims

This PhD set out with the aim of building on the studies identified within the initial systematic review and exploring the psychobiological effects of participatory music interventions both across individual sessions and longitudinally on different health populations. Four studies were successfully undertaken: three within the Mental Health Project and one with Tenovus Cancer Choirs. This involved a total of 340 active participants in 53 workshops in London and across Wales. All studies reached recruitment targets and were conducted to schedule. Data were collected and analysed as planned. Importantly, participants taking part in the interventions reported high levels of enjoyment with no complaints against the conduct of the studies.

Regarding the specific aims of the study:

Primary: To examine the effect of music interventions on both psychological and biological response

All four studies combined a range of psychological and biological measures including both state and trait assessment tools, including a total of 15 biomarkers and 8 validated scales.

Secondary: (a) To use multiplex testing to analyse a broad range of biomarkers and formulate hypotheses on the biological pathways being activated

Multiplex analysis was undertaken in partnership with Aeirtec Laboratories. The CEO of the laboratories, Dr Stephen Kilfeather, provided lab training over all three years of the PhD so that I was able to help in the analysis of the samples myself. Hypotheses on the biological pathways being affected were formulated across all four studies and tested in particular with study 2 in the Mental Health Project.

(b) To explore the changes in psychological and biological response following a single music session

Single sessions were tested in three of the four studies with a total of 295 participants across 25 separate workshops.

(c) To explore the cumulative effect of music sessions over several weeks on psychobiological response

Studies 1 and 2 of the Mental Health project examined the cumulative effect of music sessions at both 6 and 10 weeks, with follow up from the latter study suggesting the benefit of longer interventions.

(d) To examine the correlations between perceived alterations in mood with molecular biomarkers

Correlations were explored in all four studies between different state and trait psychological markers and biomarkers.

(e) To ascertain how long-lasting effects of sessions can be following the end of an intervention

Study 2 of the Mental Health project analysed the persistence of effects for 3 months following a 10-week drumming intervention.

Consequently, this PhD fulfilled the aims it set out to achieve.

7.2 Hypotheses

Regarding specific hypotheses, at the start of this PhD, I hypothesised:

H1: *There will be an increase in positive psychological affect, decrease in stress response and increase in immune-enhancing activity evident immediately after a single session of music making*

This was shown clearly in both study 1 of the Mental Health Project and in the Tenovus project. There was a significant decrease in cortisol across individual session in both studies and increases in a range of cytokines and chemokines. In the Mental Health project, this result was shown to be stronger when participants had prior experience of the music intervention with consequences for the design of future research studies.

H2: *There will be a decrease in stress response and decrease in pro-inflammatory activity over multiple sessions of music making*

There was evidence towards this in study 1 of the Mental Health project with decreases in four pro-inflammatory cytokines. In study 2, there was evidence of a shift towards an anti-inflammatory immune profile. However, there was no evidence in either study that cortisol decreased longitudinally. One potential explanation is that some participants had chronic stress and glucocorticoid resistance which meant that a relaxation response across several weeks was actually evidenced by an increase in cortisol levels at certain time-points during the day as flattened cortisol curves reassumed a more regular diurnal cycle (Juruena et al., 2003). Future studies assessing cortisol levels across the diurnal cycle will be needed to explore this hypothesis further.

H3: Decreases in levels of pro-inflammatory biomarkers will correlate with decreases in depressive symptoms

Study 1 and 2 of the Mental Health project demonstrated significant decreases in pro-inflammatory markers alongside decreases in depressive symptoms. However, there were no official correlations between these psychological and biological responses. It is possible that the timing of the data collection confounded the chance of finding correlations as samples were taken immediately before and after sessions, whereas perhaps leaving a gap of 10-15 minutes would have provided more chance for possible lag times in biological response. However, it is also possible that the psychological scales were not sensitive to the specific aspects of depressive symptoms that were linked with decreases in inflammatory response. In the Tenovus study, there was a negative correlation between short-term improvements in mood and pro-inflammatory response. But this latter finding remains to be explored longitudinally as well to assess if the pattern becomes stronger.

H4: Psychological changes will be sustained for the three months following the end of the intervention

This hypothesis was clearly evidenced in study 2 of the Mental Health Project in which the significant changes noted in anxiety, depression, social resilience and mental wellbeing were maintained 3 months following the end of the intervention. What is unknown is whether these results lasted even longer following this. However, it points to the potential sustainability of psychological results and opens up questions regarding whether underlying biological results could be maintained too.

H5: Physically making music will lead to a greater modulation in emotion than watching or listening to music

This hypothesis was tested in study 3 of the Mental Health Project, with evidence that making music lead to greater modulation of several different emotions, including happiness, than watching, listening or an audio control. There was also data to suggest that making music led to greater potency, valence and arousal as measured by semantic differential scales. However, both the between-subject design and the within-subject design suggested that watching and listening also lead to some effect on participants, simply not as great an effect as the combined components of making music.

H6: Short-term changes in emotions will correlate with biological activity

There was limited data to support this theory from study 1 or 2. Although parallel changes were found, these did not show in correlation analyses, perhaps due to a small sample size. However, in study 3 there was evidence that music-induced emotions were associated with some biological activity, particularly relating to the markers cortisol and TNF-α. In study 4, there was much more data to support this theory, with a range of correlations between specific emotions and specific biomarkers as well as suggestions that improvements in positive emotions are associated with reduced pro-inflammatory response.

Broadly, the initial hypotheses did prove to be supported by the studies within this PhD. However, there were some variations on the initial theories that point to psychobiological responses to music interventions being complex. New hypotheses for these variations have been advanced in discussing the studies presented in this PhD and these complexities will no doubt be elucidated by further research.

7.3 Contribution to the field

At the beginning of this PhD, the systematic review undertaken revealed 63 studies looking at the biological impacts of music interventions, involving 37 different biomarkers. This PhD has contributed to this body of knowledge by:

a. Adding additional studies, of which 3 would have met the initial inclusion criteria on the systematic review
b. Specifically focusing on live interventions, of which there had been only 8 studies previously, and only 2 exploring drumming and 1 exploring singing
c. Expanding the number of biomarkers tested in a single music study from 8 to 13, and specifically the number of cytokines from 4 to 9
d. Expanding the range of biomarkers tested, adding IL-17, TNF-β, MCP-1, sIL-2rα, sTNFr1 and GM-CSF and bringing the total to 43 biomarkers known to be affected by music.

In addition, this PhD can be seen to have contributed in three different research areas:

Psychobiology: These studies have been the first to examine the biological effects of a music intervention for mental health, with results suggesting that music has potential as a psychosocial intervention, although more work remains to be undertaken. Specifically, identification of the anti-inflammatory effects of group music-

making aligns this activity with other psychosocial as well as psychological and pharmacological interventions regarding the biological pathways that appear to be modulated (Slavich & Irwin, 2014). In the past few years, certain psychosocial interventions, such as mindfulness, have moved into the mainstream of psychobiological research as studies exploring their impact have demonstrated their efficacy as adjuncts to conventional treatments. Such interventions are now a common feature in conferences and journals (Chiesa & Serretti, 2010; Greeson, 2009; Hofmann, Sawyer, Witt, & Oh, 2010). The evidence presented here suggests that music interventions could be another valuable tool for mental health. Further research will be needed to explore this more, including examining the biological pathways activated by music in more specific mental health conditions, looking more at the long-term biological effects including biological follow-up and testing other music-based interventions. However, it is plausible that music interventions too could become more common research topics within the field.

Music psychology: From within the broader area of research into music interventions, there are still relatively few studies that have looked at longitudinal effects of interventions on psychological response. Many interventions active in the UK and abroad report predominantly qualitative data or conduct service evaluations without controlling for many of the potential confounding variables. However, the first two phases of the Mental Health Project have demonstrated the long-term of impact of group music-making among one patient group on a range of psychological constructs, including depression, anxiety, social resilience and mental wellbeing, as well as follow-up benefits after an intervention has finished. This is promising evidence suggesting the value of longitudinal studies in other areas of music psychology research. Furthermore, the topic of music and emotion is very popular within music psychology (Juslin & Sloboda, 2011). The correlations presented in this PhD between emotions and biological markers suggest that the inclusion of biomarkers in future studies could further extend understanding around the personal psychological effects of music.

Evolutionary musicology: It is also of note that all four studies showed that a music intervention can modulate components of the innate immune system (demonstrated in MCP-1) as well as cytokines within the adaptive immune systems. The initial systematic review of the psychoneuroimmunological effects of music showed that prior to these two studies, only components of the adaptive immune system had been examined previously (Fancourt et al., 2014), although two studies have explored the effects on Natural Killer cells (B. B. Bittman et

al., 2001b; Leardi et al., 2007b). In attempting to refute the view that music does not have an evolutionary role and is instead 'auditory cheesecake' (Pinker, 1999), music psychologists and ethnomusicologists have proposed theories on music's role in evolution, including its function in social cohesion and intra-group bonding, attraction of mates, and mother-infant interactions (Buss, 2005). However, another possible avenue is that music has an evolutionary role to play in stress reduction and immune optimization. The evidence presented in this PhD of the ability of music to modulate components of the ancient innate immune system as well as the more recently developed adaptive immune system is preliminary, but suggests that the theory could be worth exploring. Future studies may be able to examine whether other components of the innate immune system are involved in biological responses to music and whether this leads to hypotheses of an evolutionary role of music in immune regulation.

7.4 Limitations

There were a number of limitations to this PhD. Many of these have been discussed in relation to the specific studies. However, a few broad limitations remain. Patients in all four studies were from a broad demographic including different age groups and ethnicities. Participants in the Mental Health Project had a range of mental health diagnoses, and were at varying stages of treatment (although importantly they did not undergo any changes in treatment while involved in the studies). Regarding participants in the Tenovus studies, we chose only to formally analyse the data of the patients in remission as it was felt that the patients had too broad a range of diagnoses. All of these participant demographics were clearly reported in the studies and the inclusion and exclusion criteria were a conscious decision in order to reflect the 'community' aim of these music interventions.

There was also a natural bias in participant recruitment towards participants self-selecting to take part. Participants were not obliged to sign up to the studies as part of their treatment but were offered the interventions. Especially for the Mental Health project, although many participants reported limited experience with music, and specifically no previous experience of group drumming, they still selected to take part in a multi-week project which suggests an interest in the activity. Consequently, it remains unknown whether the interventions explored would have had the same impact on participants who disliked drumming. Furthermore, participants were aware that the aim of the drumming project was to support their mental

wellbeing. As such, a placebo effect is likely to have been present to some extent, especially due to the common rhetoric around the 'healing' benefits of music. Results were statistically significant, in some cases replicated, included some large effect sizes (for example, as great as 38% reductions in depression). They were also found to be maintained after 3 months of not receiving an intervention in study 2, which suggests that there may be more than just a placebo effect occurring. Furthermore, in the real world setting, this issue of self-selection exists for a range of mental health treatments, including both pharmacology and psychotherapy where participants opt to receive them. As such, this study was representative of a real-world scenario in that participants were offered the choice of the intervention and signed up if they thought it would be of benefit to them. However, the results should be interpreted in light of this limitation.

Finally, the use of saliva analysis is still a relatively new field. As discussed, there is growing evidence to support its use with increasing research attesting to its reliability (Byrne et al., 2013; Williamson et al., 2012). The analysis undertaken in this PhD was carried out with Aeirtec Laboratories, who have over 20 years' experience in running clinical trials and undertake analysis for some of the leading pharmaceutical companies, including Pfizer and Astra-Zeneca. They follow GLP and ISO 17025 principals and are externally audited by a Quality Assurance company TMQA as well as the US biotech industry and Pfizer pharmaceuticals. The inter-assay coefficient of variation range for all analytes was 1.8-5.37% and the intra-assay coefficient of variation range was 0.8-3.58%, attesting to the high quality of the analysis. However, this does not detract from the limitation that blood analysis is still regarded as the gold standard. As such, these results cannot be directly compared with studies that used blood analysis and results should be interpreted with an appropriate level of caution.

For future studies, it would be interesting to take forwards drumming interventions for mental health and explore their effects on more specific mental health populations. In order to increase the rigour, a randomised controlled design would be advised, involving a larger sample size. Ideally, a three-arm study would be developed that included an active comparison group (such as support meetings) and a control group without intervention exposure. Considering both stress hormones and the balance of pro- and anti-inflammatory markers appears to be of value. For the mechanistic work, a larger scale study would be needed that included an adequate sample size to consider both psychological and biological markers. Based on the data from the initial study presented here, it may be possible to reduce the number of psychological scales used in order to

increase the level of p that would be considered significant. For example, following the model of the Tenovus study, it may be possible to focus specifically on mood and stress as two meta-variables rather than 12 individual variables. Adding in a comparison activity that involved exercise and expanding the initial tiered 4-intervention design to include different combinations of the four key components would be revealing scientifically, but would increase the difficulties in recruiting adequate numbers of participants so there would need to be a balance struck between having enough test conditions and including enough variables to identify where change occurs. For the cancer choir work, based on the promise of the initial data, it would be interesting to take this forwards with a longitudinal study again specifically exploring certain patient groups as well as distinguishing between professional carers (such as hospital staff) and informal carers (both current and bereaved). For all studies, it would be particularly pertinent to be able to consider blood as well as saliva analyses, but this would of course pose not insignificant financial and logicistal challenges. Nevertheless, it is hoped that these initial studies will pave the way for future work in this area.

7.5 Implications

It is hoped that this PhD will have several implications:

From a **psychobiological perspective**, it is hoped that with the publication of these results in mainstream psychobiological journals such as *Psychotherapy and Psychosomatics* and their presentation at conferences such as the American Psychosomatic Society, music interventions will be taken as the subject of future studies. In the same way that mindfulness research has really expanded in the past few years, it is hoped that these studies will support the growing scientific interest in music-based interventions.

From a **clinical perspective**, this project involved engaging over 30 clinical psychologists and other healthcare professionals in London. Although many had not previously worked with music interventions for their patient groups, there has been a very positive reception to the project and its results. Already, three other psychologists from other healthcare trusts in London, Gloustershire and Hertfordshire have asked to be involved in future studies, all of which are now being followed up for new research project ideas. The drumming intervention used in the Mental Health Projects has been taken forwards in the Borough of Richmond as a community service for mental health patients, and it has been selected as one of the new innovation projects by Breathe, a spin-out organisations of Guy's and St Thomas' Hospital who develop

creative healthcare interventions to be suitable for funding from Clinical Commissioning Groups. Consequently, it is hoped that these PhD studies will support the spread of community music activities aimed at mental health service users and specifically the engagement of psychology professionals in this process to ensure the quality and suitability of the interventions for service users.

From an **arts perspective**, there are an increasing number of white papers discussing the potential of music interventions for both health and wellbeing (Fujiwara, Kudrna, & Dolan, 2014; Mark Newman, 2010; RSPH, 2013). The studies in this PhD have been included in a portfolio discussed in a number of these forums, including the Royal Society for Public Health steering group on arts, health and wellbeing, at the Academy of Medical Sciences music and medicine public engagement event, and with members of parliament, including the previous Minister for Culture, Media and Sports. In particular, the evidence of the longitudinal impacts of music making and the follow-up effects are of value in considering potential financial benefit of investing in fixed-term interventions. It is hoped that the discussion of these studies will support future funding for such community programmes. Indeed, the evidence from the Tenovus study has already been used in two large-scale future funding bid to spread the Tenovus choirs from Wales into England, with the first choir starting in London in 2016 funded by Novatis pharmaceuticals.

From an **individual perspective**, 340 individuals with mental health conditions have been given access to free music workshops as part of this PhD. Anecdotally, there have been many cases of these participants reporting the benefits they have felt, which two further qualitative studies undertaken by other researchers have explored in more detail. This PhD also involved training 8 early-career musicians to lead the music sessions. Of these, all 8 demonstrated improvements in their own mental wellbeing (evaluated for interest using the same psychological scales but not reported here). Two of them have now changed their career plans to focus more on this work, one going into community music leadership and another retraining as a music therapist. The Royal College of Music is now using the results from this study as evidence to increase its community provision and student training for similar future projects.

Finally, from a **research perspective**, this PhD has led to several follow-on research grants being awarded, including:

- Sing With Us II: the effects of singing on psychological and immune response in cancer patients and carers, *Tenovus Cancer Care*, January 2016 – January 2018, £250,000, PI: D Fancourt & T Wiseman, CI: A Williamon
- Singing Away the Blues: the psychobiological effects of singing on postnatal depression, *Arts Council Research Grants Fund*, June 2015 – March 2017, £199,916, PI: R Perkins, CI: D Fancourt
- Art for Ages: psychobiological wellbeing in older adults in Southern Switzerland, *BREF, Gebert Rüf Stiftung,* May 2015 – May 2017, £220,000, PI: A Williamon, CI: H Eiholzer, P Di Giulio, S Cavalli, D Fancourt

These all build on the findings of this PhD and will hopefully increase the knowledge around the psychobiological impacts of arts-based interventions in healthcare and encourage their application in clinical and community settings.

7.6 Closing remarks

This PhD has provided evidence to suggest that music making interventions can have psychological benefits for participants with either primary or secondary mental health conditions along with modulations of associated biological response. The endocrine and immune changes found are in line with those found in other pharmacological, psychological and psychosocial studies. The fact that these interventions are delivered in groups and results have been demonstrated to be sustainable following longer interventions suggests that group music interventions could be practical and potentially cost-effective as a mental health intervention alongside other treatments. This could encourage the development of more community music interventions for mental health. Indeed, as pilot studies are commencing in the UK and other countries into cultural commissioning, whereby arts interventions are being funded alongside traditional medical interventions within health care budgets, this evidence may have a role to play in providing support for such initiatives and informing the design of future evaluation and research projects. It is hoped that planned post-doctoral research will reveal more about the mechanisms underlying these responses and the significance of their impact on health conditions.

8 PUBLICATIONS AND PRESENTATIONS

Selected papers:

Fancourt D, Lewis I, Dow R, Carvalho LA, Steptoe A, & Williamon A (2016), Singing modulates mood, cortisol, oxytocin, beta-endorphin and cytokine activity in cancer patients and carers, *ecancer*

Fancourt D, Perkins R, Ascenso S, Kilfeather S, Carvalho LA, Steptoe A, & Williamon A (2016), Effects of group drumming interventions on anxiety, depression, social resilience and inflammatory immune response among mental health service users, *PLOS ONE*

Fancourt D, Perkins R, Ascenso S, Atkins L, Kilfeather S, Carvalho LA, Steptoe A, & Williamon A (2015), Group drumming modulates cytokine response in mental health service users: A preliminary study, *Psychotherapy and Psychosomatics*.

Fancourt D, Aufegger L, & Williamon A (2015), Low-stress and high-stress singing have contrasting effects on glucocorticoid response, *Frontiers in Psychology*, 6: 1242.

Fancourt D (2015), Birds, apes, and grandmothers: The personal side of music and health research, *PsycCRITIQUES*, 60(18).

Fancourt D, Joss, T, (2015) Aesop 1: a methodological framework for arts and health research programmes *International Journal of Arts and Health: Research, Policy and Practice*, 7(1): 1-13.

Fancourt D (2014, online first) An introduction to the psychoneuroimmunology of music:
history, future collaboration and a research agenda *Psychology of Music*

Fancourt D, (2014) Music, Health and Wellbeing: a review, *Psychology of Music*

Fancourt D, Ockelford A and Belai A, (2014) The Psychoneuroimmunology of Music: A Systematic Review and New Model *Brain, Behaviour & Immunity* 36: 15-26.

Fancourt D (2013), Medicine Musica: Two lenses on the rationalization of music and medicine, *Hektoen International, 5 (3)*

Posters:

22-26 June 2014 Music and Psychoneuroimmunology, *International Association for Music and Medicine Conference,* Toronto, Canada

Conferences:

26 November 2015	Music, health and hospitals (guest lecturer), *FHS2015-16*, University of Oxford
4 November 2015	Can music change our immune function? (invited speaker) *Centre for Music and Science, University of Cambridge*
3 September 2015	Psychobiological responses to drumming in mental health patients, *International Symposium for Performance Science*, Kyoto, Japan
18 August 2015	Biological response underpins music-induced emotions *European Society for the Cognitive Sciences of Music*, Manchester
11 July 2015	Does singing affect your health? (invited speaker) *Cheltenham Music Festival*, Cheltenham
22 April 2015	The clinical application of music (invited speaker) *Psychology department, Oldenberg University*, Germany
21 March 2015	Psychobiological responses to group drumming interventions, *American Psychosomatic Society,* Savannah, Georgia
18 March 2015	Music, motherhood and mental health, Young Investigator Colloquium, *American Psychosomatic Society,* Savannah, Georgia
17 October 2014	An introduction to music and health (invited speaker), *FHS2014-16*, University of Oxford
10 September 2014	The effect of singing on molecular biomarkers (invited speaker), *International Singing and Health Symposium*, Royal College of Music, London
22-26 June 2014	Making Music for Mutual Recovery, *International Association for Music and Medicine,* Toronto, Canada
20 June 2014	Music for cognitive rehabilitation (invited speaker) *Music, Emotions and Wellbeing Symposium,* Wellcome Trust and Queen Mary's University, London
4 June 2014	The biology of music and mental health (invited panel member) *Music, Society and Mental Wellbeing*, Nordoff Robbins, London

20 March 2014	Music and medicine in the NHS (invited speaker), *Music and Medicine Event*, Academy of Medical Sciences, London
12 March 2014	Music and medicine through the lifespan (invited speaker), Institute for Population Aging, University of Oxford
6 December 2013	Music & Mental Health (invited speaker), *Centre for Social Futures Launch*, University of Nottingham
19 October 2013	Music Psychology and Biology: multidisciplinary, interdisciplinary or transdisciplinary? *Music, Health and Ethics Conference* SEMPRE/BFE/Goldsmith's College, London
6 June 2013	Towards A Theoretical Model of Music and Psychoneuroimmunology *Making A Difference With Research Conference,* Roehampton University London

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APPENDIX 1 – Overview of biomarker function

Biomarker	Function
Cortisol	Is a steroid hormone of the glucocorticoid class released in response to corticotropin-releasing hormone and adrenocorticotropin-releasing hormone in the brain. It has anti-inflammatory properties (Cline & Melmon, 1966).
GM-CSF	Is a colony-stimulating factor secreted by a range of leukocytes that functions as a cytokine. In particular, it stimulates stem cells to differentiate into granulocytes and monocytes (Francisco-Cruz et al., 2014).
IFN-γ	Is a pro-inflammatory cytokine expressed predominantly by natural killer cells and T lymphocytes. It is important for both innate and adaptive immune responses, such as activating macrophages (Schoenborn & Wilson, 2007).
IL-10	Is an anti-inflammatory cytokine. It enhances B cell survival, proliferation and antibody production and can repress pro-inflammatory responses (Ouyang, Rutz, Crellin, Valdez, & Hymowitz, 2011).
IL-17	Is involved in inducing and mediating pro-inflammatory responses, such as IL-6, GM-CSF, TNF-α and MCP-1 in a range of innate immune cells. It has also been linked specifically to allergies and auto-immune diseases (Aggarwal & Gurney, 2002; Jin & Dong, 2013).
IL-2	Is involved in promoting the differentiation of immature T cells into regulatory T cells, memory T cells and effector T cells. It also plays an important role in regulating immune responses through negative feedback loops (Liao, Lin, & Leonard, 2011; Malek & Castro, 2010).
IL-4	Is an anti-inflammatory cytokine involved in stimulating activated B-cell and T-cell proliferation, the differentiation of B cells into plasma cells and up-regulation of MHC class II production. IL-4 also decreases the production of macrophages and some pro-inflammatory cytokines such as IL-12 and IFN-γ (Choi & Reiser, 1998).
IL-6	Is secreted by leukocytes of both the innate and adaptive immune systems and has an immune-stimulating effect. However, it also inhibits certain pro-inflammatory cytokines such as TNF-α and IL-1. Importantly, IL-6 is capable of crossing the blood-brain barrier where it interacts with neurotransmitters such as serotonin (Scheller et al., 2011, p. 6; Stojanovic et al., 2014, p. 6).
MCP-1	Is a chemokine that recruits leukocytes including monocytes, dendritic cells and memory T cells to sites of inflammation (Carr et al., 1994).
Oxytocin	Is a neuropeptide produced in the hypothalamus and stored in the pituitary gland. It is involved in social bonding as well as stress responses and a number of physiological processes (Bartz et al., 2011; Olff et al., 2013).
sIL2rα	(Also known a CD25) is expressed by T and B lymphocytes. It has been found to be elevated in patients with depression (Allen-Mersh et al., 1998)
sTNFr1	Is expressed on a range of leukocytes. sTNFr1 is a marker of inflammation and has been found to be elevated in patients with depression. (Grassi-Oliveira et al., 2009, p. -)
TGF-β	Plays a regulatory role. It promotes the induction of regulatory T cells in the thymus and in the periphery (Bird, 2010; Sanjabi et al., 2009).
TNF-α	Is a pro-inflammatory cytokine. It plays an important role in the regulation of leukocytes as well as inducing apoptotic cell death and inflammation (Hickey et al., 1997). Dysregulation has been found in a range of conditions from depression to Alzheimer's to cancer (Dowlati et al., 2010; Swardfager et al., 2010).
β-endorphin	Is a neuropeptide and one of five endorphins in humans. It has analgesic properties and has also been associated with feelings of elation (Dubois et al., 1981; Guillemin et al., 1977; Øktedalen et al., 2001).

APPENDIX 2 – Psychological scales

Warwick Edinburgh Mental Wellbeing Scale

Please tick the box that best describes your experience of each over the last month.

Statements	None of the time	Rarely	Some of the time	Often	All of the time
I've been feeling optimistic about the future					
I've been feeling useful					
I've been feeling relaxed					
I've been feeling interested in other people					
I've had energy to spare					
I've been dealing with problems well					
I've been thinking clearly					
I've been feeling good about myself					
I've been feeling close to other people					
I've been feeling confident					
I've been able to make up my own mind about things					
I've been feeling loved					
I've been feeling interested in new things					
I've been feeling cheerful					

Hospital Anxiety and Depression Scale

Read each item below and tick the reply which comes closest to how you have been feeling over the past month. Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

I feel tense or 'wound up'

Most of the time
A lot of the time
From time to time, occasionally
Not at all

I still enjoy the things I used to enjoy

Definitely as much
Not quite so much
Only a little
Hardly at all

I get a sort of frightened feeling as if something awful is about to happen

Very definitely and quite badly
Yes, but not too badly
A little, but it doesn't worry me
Not at all

I can laugh and see the funny side of things

As much as I always could
Not quite so much now
Definitely not so much now
Not at all

Worrying thoughts go through my mind

A great deal of the time
A lot of the time
Not too often
Very little

I feel cheerful

Never
Not often
Sometimes
Most of the time

I can sit at ease and feel relaxed

Definitely
Usually
Not often
Not at all

I feel as if I am slowed down

Nearly all the time
Very often
Sometimes
Not at all

I get a sort of frightened feeling like 'butterflies' in the stomach

Not at all
Occasionally
Quite often
Very often

I have lost interest in my appearance

Definitely
I don't take as much care as I should
I may not take quite as much care
I take just as much care as ever

I feel restless as if I have to be on the move

Very much indeed
Quite a lot
Not very much
Not at all

I look forward with enjoyment to things

As much as I ever did
Rather less than I used to
Definitely less than I used to
Hardly at all

I get sudden feelings of panic

Very often indeed
Quite often
Not very often
Not at all

I can enjoy a good book or radio or television programme

Often
Sometimes
Not often
Very seldom

Connor-Davidson Social Resilience Scale

The statements below are about how you respond to situations. For each item, tick the box that best indicates how much you agree with the following statements as they apply to you over the last month. If a particular situation has not occurred recently, answer according to how you think you would have felt.

Statements	Not true at all	Rarely true	Some-times true	Often true	True nearly all the time
I am able to adapt when changes occur					
I have at least one close and secure relationship that helps me when I am stressed					
When there are no clear solutions to my problems, sometimes fate or God can help					
I can deal with whatever comes my way					
Past successes give me confidence in dealing with new challenges and difficulties					
I try to see the humorous side of things when I am faced with problems					
Having to cope with stress can make me stronger					
I tend to bounce back after illness, injury or other hardships					
Good or bad, I believe that most things happen for a reason					
I give my best effort no matter what the outcome may be					
I believe I can achieve my goals, even if there are obstacles					
Even when things look hopeless, I don't give up					
During times of stress/crisis, I know where to turn for help					
Under pressure, I stay focused and think clearly					
I prefer to take the lead in solving problems rather than letting others make all the decisions					
I am not easily discouraged by failure					
I think of myself as a strong person when dealing with life's challenges and difficulties					
I can make unpopular or difficult decisions that affect other people, if it is necessary					
I am able to handle unpleasant or painful feelings like sadness, fear and anger					

In dealing with life's problems, sometimes you have to act on a hunch without knowing why					
I have a strong sense of purpose in my life					
I feel in control of my life					
I like challenges					
I work to attain my goals no matter what roadblocks I encounter along the way					
I take pride in my achievements					

Perceived Stress Scale

The statements below are about how you cope with things. For each item, tick the box that best indicates how much you agree with the following statements as they apply to you over the last month. If a particular situation has not occurred recently, answer according to how you think you would have felt.

Statements	Never	Almost never	Sometimes	Fairly often	Very often
In the last month, how often have you been upset because of something that happened unexpectedly?					
In the last month, how often have you felt that you were unable to control the important things in your life?					
In the last month, how often have you felt nervous and "stressed"?					
In the last month, how often have you felt confident about your ability to handle your personal problems?					
In the last month, how often have you felt that things were going your way?					
In the last month, how often have you found that you could not cope with all the things that you had to do?					
In the last month, how often have you been able to control irritations in your life?					
In the last month, how often have you felt that you were on top of things?					
In the last month, how often have you been angered because of things that were outside of your control?					
In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?					

Secker Social Inclusion Scale

The statements below are about your relationships with other people.

Please tick the box that best describes your experience over the last month.

Statements	Not at all	Not particularly	Yes a bit	Yes definitely
I have friends I see or talk to every week				
I have learnt something about other people's cultures				
I have been to new places				
I have felt accepted by my friends				
I have felt accepted by my family				
I have felt accepted by my neighbours				
I have been out socially with friends				
I have done some cultural activities (e.g. gone to a library, museum, gallery, theatre, concert)				
I have felt clear about my rights				
I have felt free to express my beliefs (for example political or religious beliefs)				
I have felt that I am playing a useful part in society				
I have felt that what I do is valued by others				

Visual Analogue Scales

Thank you for taking part in the workshop! How do you feel right now? (place a line on the scale)