The Neurochemistry of Instrumental Improvisation in Adults: A Feasibility and Pilot Study

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ABSTRACT

This study examined the molecular underpinnings of group instrumental music improvisation as well as verbal improvisation in musicians and nonmusicians using blood-based measurements of oxytocin, vasopressin, dopamine, and cortisol, with verbal improvisation serving as a control. All participants (N = 8) were able to successfully complete study tasks as directed and tolerate the blood draws. On average, regardless of musicianship status, males had a greater and directionally divergent change in cortisol when compared to females (males $M = -.033$; females $M = .025$) after improvising musically ($p < .04$). Males also had a significant difference between the decrease in cortisol after music improvisation ($M = -.033$) compared to an increase in cortisol after verbal improvisation ($M = .026$; $p < .01$). The current investigation provided promising results regarding the ability of the study design and procedures to yield useful information when bringing the study to scale with a sufficiently powered sample indicating potential sex and modality based differences.

KEYWORDS

music
neurochemical
improvisation
bonding
oxytocin

INTRODUCTION AND LITERATURE REVIEW

A great deal of attention has been given to understanding of the neuroanatomical basis for musical behavior, namely, the identification of regions of the brain involved in discrete elements of music such as rhythm (Koelsch, 2019; Levitin & Tirovolas, 2009), whereas considerably less is known about the neurochemistry of music perception and production. Chanda and Levitin (2013) argued that studies of the neurochemistry of musical behavior are likely to provide greater mechanistic explanatory power than neuroanatomical studies, particularly with regard to the effects of music on health outcomes, including health-related quality of life. One neurochemical study (Keeler et al., 2015), on which the current study was based, identified the neuropeptide oxytocin (OT) and adrenocorticotropic hormone (ACTH) as key interacting contributors to feelings of social affiliation, bonding, and trust often reported as outcomes of group music-making, which could contribute to health-related quality of life. It demonstrated that the design and procedures used were feasible to elicit and detect changes in OT and ACTH, that singing seemed to create reductions in stress, and that the production of OT is idiosyncratic and varied between rote and improvised singing. This was an important design decision as most studies of music using neurochemical outcomes employ rote music making interventions, thus, the novelty of the current study was its use of improvised music and verbal exercises.

Neurochemistry

OXYTOCIN AND VASOPRESIN

OT and vasopressin, also referred to as arginine vasopressin (AVP) are known to regulate social behavior (Johnson & Young, 2017; Meyer-Lindenberg et al., 2011) and are considered to be reasonable candidates in the mediation of the social effects of music (Chanda & Levitin, 2013). Typically thought of as involved in mother-infant bonding (Numan & Young, 2016), and often referred to as the love or hug hormone in popular culture (Shen, 2015), developing evidence suggests that OT's regulation of social behavior depends on both social context and individual

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traits (Bartz, 2016; Bartz et al., 2011). As such, OT by itself should not be considered prosocial. Rather, in conjunction with other hormones, context, and individual characteristics, OT likely increases perception of social behaviors (Bartz, 2016) and helps to regulate stress by increasing the motivation for social contact and support within the context of psychotherapy (Cardoso et al., 2016; Taylor et al., 2000). The role of AVP is also thought to mediate social behavior, including the social effects of music, but is less understood (Insel, 2010). One function of AVP that has been observed is that it mediates facial expression and ratings of friendliness, and has effects that differ by gender, where men react negatively to the faces of unfamiliar men but women react positively to the faces of unfamiliar women (Thompson et al., 2006). It is clear that AVP and OT interact to mediate social behavior in human and nonhuman mammalians (Insel, 2010; Johnson & Young, 2017; Meyer-Lindenberg et al., 2011). This includes musical behavior, as AVP has been observed to mediate musical memory (Granot et al., 2007) and is associated with musical aptitude as it relates to attachment behavior (Ukkola et al., 2009), such as the use of lullabies to attach infants to mothers (Fancourt & Perkins, 2017, 2018; Persico et al., 2017; Robertson & Detmer, 2019) and making music to increase group cohesion (Boer & Abubakar, 2014; Koelsch, 2013). Relatedly, the brain opioid theory of social attachment suggests that OT, AVP, and dopamine (DA) contribute to the development of social bonds, and the feelings of dependence that are required for humans to maintain relationships are likely instigated by endogenous opioids (Chelnokova et al., 2014; Machin & Dunbar, 2011; Pearce et al., 2015; Tarr et al., 2014).

DOPAMINE

The contribution of DA to social behavior is likely due to the pleasure and reward one experiences associated with increases in DA secretion (Dubé & Le Bel, 2003; Egerton et al., 2009). So-called naturally rewarding stimuli (e.g., food and sex) also result in dopaminergic activity in either/both the ventral tegmental area (VTA) and nucleus accumbens (NAc, Alonso-Alonso et al., 2015; Pfaus et al., 1995), as do drugs that possess addictive properties (Volkow et al., 2017). Fascinatingly, music has also been demonstrated to activate dopaminergic neurons in the mesolimbic pathway including the VTA and NAc (Blood & Zatorre, 2001; Menon & Levitin, 2005). Further differentiation was observed in pathways between the anticipation (caudate nuclei) and experience (NAc) of peak emotional reward from listening to music (Salimpoor et al., 2011). A causal relationship has been observed between music and hedonic experience. When compared to a placebo (lactose), the administration of a dopamine precursor (levodopa) prior to music listening increased the hedonic experience and motivational response, whereas the administration of a dopamine antagonist (risperidone) resulted in a reduction in both (Ferreri et al., 2019). So, the timeline of approaches described above examining the relationship between music and dopamine was to first use positron emission tomography (PET) imaging to examine activity in reward circuitry related to music listening (Blood & Zatorre, 2001). Then, craclopride PET, a technique that allows for estimating dopamine release in cerebral tissue (Salimpoor et al., 2011), was used to show activity in dorsal and ventral striatum, bilaterally. Thirdly, functional magnetic resonance imaging (fMRI) was used to observe the relationship between the NAc and music listening (Salimpoor et al., 2013). Finally, Ferreri et al. (2019) pharmacologically manipulated a dopaminergic agonist and antagonist and observed differential responses to the perceived pleasure of music listening. The current study sought to explore the feasibility of the use of blood assays as a method of examining dopaminergic activity as a result of active music making.

CORTISOL

Cortisol is perhaps the most well understood hormone related to stress and is known to prepare the body for a fight or flight scenario by increasing the amount of available glucose in the bloodstream and attenuating nonessential functions (Dedovic et al., 2009). However, sustained productivity of cortisol (which is secreted in the zona fasciculata layer of the adrenal cortex just above the kidneys) is associated with deleterious effects on social, emotional, and cognitive function and related physiological systems (Chrousos, 2009). Musical behavior has been observed to mediate the secretion of cortisol, where salivary cortisol did not increase as a result of listening to music compared to silence (Khalfa et al., 2003), group singing resulted in a decreases in cortisol for people with cancer (Fancourt, Williamon, et al., 2016; Warran et al., 2019), and group drumming resulted in nonsignificant reductions of cortisol in people receiving mental health services for anxiety and/or depression (Fancourt, Perkins, Ascenso, Carvalho, et al., 2016). The interaction between endogenous oxytocin and cortisol is poorly understood and seems context-dependent, particularly in social situations (Brown et al., 2016; Schladt et al., 2017). What is becoming more evident over the last two decades of research is that the brain structures involved in these neurochemical processes seem to differ based on the intensity and duration of musical training..

Musicians Versus Nonmusicians

Gaser and Schlaug (2003) observed that professional musicians had significantly greater gray matter in regions associated with auditory, motor, and visuospatial functioning when compared to amateur musicians and nonmusicians. Acer et al. (2018) also observed differences in brain structure between professional musicians and nonmusicians, particularly in the grey matter of both hemispheres of the cerebellum, supramarginal and angular gyri, left superior and inferior parietal lobe, and left middle temporal gyrus. Using a different approach to understand whether differences in musicians and nonmusicians was attributable to training, Hyde et al. (2009) observed that children who received 15 months of musical training demonstrated increases in relative voxel size in areas such as motor and auditory cortices as compared to children who did not receive such training. The two groups of children had no structural brain differences at the onset of training, suggesting that exposure to music instruction, even for a relatively brief time, structurally reorganizes the brain.

Although comparisons between musicians and nonmusicians appear in the extant scientific literature, to date, there is no universally agreed-upon definition that is used to stratify by musical ability when comparing musicians to nonmusicians (Merrett et al., 2013). For instance, Gaser and Schlaug (2003) defined professional musicians as those who were engaged in full-time music making (e.g., performance artists, music teachers, and students), whose average daily practice time exceeded one hour, whereas nonmusicians were operationally defined as having never played a musical instrument. Schulze et al. (2011) similarly used university students engaged in formal music instruction as "musicians" and defined the nonmusician group as those who had no formal training. Grahn and Rowe (2009) defined musicians as having five or more years of formal musical training with ongoing musical experience and nonmusicians as having no formal training or experience. Less rigid definitions of the amount of experience required for a participant to meet the criteria of musician or nonmusician have also been used. In one study comparing percussionists and vocalists to nonmusicians, nonmusician participants were defined as having no more than three years of musical experience across their lifetime, with no participation in music making experiences in the three years prior to the study (Slater & Kraus, 2016). Another study conducted by the current author's research team used the criteria of less than one year of formal music instruction either privately or in an ensemble (e.g., school or community band) and no formal participation in music instruction or performance in the three years prior to the study to operationalize the term "nonmusician" (Bumgarner, 2015). Given that this proposed study is a pilot that compared musicians to nonmusicians, includes the feasibility of recruitment as an outcome measure, and aims to maximize outcome comparisons, the term "musician" was defined as having at least three years of formal instruction with ongoing music experience greater than one hour per day on average; nonmusicians were defined as having no formal music instruction in their lifetime nor music making experience in the three years prior to the study.

The current study aimed to contribute to better understanding the relationship between and among oxytocin, vasopressin, cortisol, and dopamine in the context of the socioemotional experience of improvised music making and verbalization. As improvisation is one of the four primary methods of music therapy (Gardstrom & Sorel, 2015) and verbal dialogue is the primary method of traditional talk-based psychotherapies (Gumz et al., 2015), it is possible that understanding the underlying biological mechanisms of these methods may contribute to improved outcomes for a large number of people seeking treatment from music therapists for mental health (MacDonald & Wilson, 2014). Music and verbal improvisation can be structured similarly in a way that resembles verbal dialogue, such that reasonable comparisons can be made to distinguish between the two approaches. Due to the relative novelty of the study design and outcome measures, this study included both feasibility and biochemistry outcome measures. The research questionswere as follows:

- Feasibility Outcomes:
  a. To what extent will we be able to recruit and enroll participants into the study?
  b. Will the participant(s) be able to understand the directions and perform the tasks as instructed?
  c. Will the participants complete the full protocol?
  d. Have we considered all necessary inclusion and exclusion criteria?
  e. Can we implement the study procedure in a timely manner to avoid or limit participant fatigue?
  f. Will the paradigms we have created yield sufficient results to make meaningful comparative analyses?
  g. Is our equipment adequate to the needs of the study?

- Neurochemical Outcomes
  a. Does improvised instrumental music interaction result in significant pre-to-post intervention changes in the following:
    i. plasma dopamine
    ii. plasma oxytocin
    iii. plasma vasopressin
    iv. plasma cortisol

  b. Does improvised verbal interaction result in significant pre-to-post intervention changes in the following:
    i. plasma dopamine
    ii. plasma oxytocin
    iii. plasma vasopressin
    iv. plasma cortisol

  c. Will there be significant differences in plasma concentrations of dopamine, oxytocin, vasopressin, and cortisol between music and non-music conditions?

METHOD

Study Design

This study used a 2 × 2 × 2 mixed factorial design that compared musicians to nonmusicians (between-groups variable), interactive improvised music versus interactive improvised verbal tasks, and pre-to-post-test comparisons (within-subject variable).

Participants

Participants were recruited from the instrumental jazz studies program at a large midwestern university and from the general student body at that same university ($N = 8$; $n = 4 \times 2$ groups; Group 1: Musicians vs. Group 2: Nonmusicians). Each participant served as their own control by participating in both the group instrumental improvisation and an isomorphic nonmusical verbal condition. Using recommendations from Kosfeld et al. (2005), exclusion criteria included smoking more than 15 cigarettes per day, drug or alcohol abuse, weighing less than 110 pounds, bleeding disorders (e.g., hemophilia), and pregnancy. Inclusion criteria for all participants included university students that were at least 18 years of age. Inclusion criteria for the musician group included the added attribute of their active student status in the university's jazz studies program which was verified by the program's chairperson.

Location of Data Collection

Study procedures and data collection, including blood sampling, took place in the university school of music library. Blood samples were obtained in a conference room inside of the library. The music improvisation intervention took place in a large office across the hall from the library and the verbal improvisation intervention took place in the same conference room where the blood draws occurred. Blood samples were received, stored, centrifuged, and analyzed in a laboratory in an adjacent building.

Recruitment and Procedure

Following approval by the university's human subjects institutional review board, a recruitment flyer was emailed to the chair of the university's jazz studies program with a request that the flyer be forwarded via email to all current instrumental jazz studies majors. Hard copies of the recruitment flyer were also provided at the end of instrumental ensemble rehearsals and used the following recruitment script: "*Our colleagues in Music Therapy are conducting a study that will investigate the neurochemistry of improvisation. If you are interested in participating or finding out more about the study, their contact information is on the flyer and you are invited to call or email sometime in the next week.*" The flyer included the email address and university phone number for the investigator and encouraged anyone interested to contact the investigator. The recruitment flyer was also placed outside of the researcher's laboratory located in a health sciences building, as well as a bulletin board in a building that hosts other scientific disciplines. Following an initial inquiry, a scripted response was sent via email inviting prospective participants to ask any questions they may have. Upon expression of interest, a consent form was sent to the prospective participant and a meeting was arranged for further clarification and signing of the consent document. All participants were consented into the study in the investigator's office.

A potential participant's appropriateness for inclusion was determined during consent signing and on a self-report basis. Once enrolled in the study, dates for data collection were arranged and the participants were asked to abstain from food and drink (other than water) two hours before the experiment. They were also asked to refrain from smoking, caffeine, and alcohol 24 hours before the experiment. All of the substances and attributes described above qualify for exclusion due to their likelihood of altering plasma concentrations of the hormones observed in this study. Participants who completed the study received an Amazon gift card in the amount of $100.

Participants were assigned to one of two groups, musicians (MUS) or nonmusicians (nonMUS), based on their musical background. To create a musical experience that was aesthetically pleasing and accessible to both groups, improvisations included clear structural guidelines. These included the use of form to guide the overall stepwise process of when individuals would play and the use of modes to restrict the actual pitches to those that are consonant with each other. See Point IV in the Stepwise Detailed Protocol section, for a detailed description. See Figure 1 for an overview of the study protocol.

Data Collection

NEUROCHEMICAL MEASURES

Data collection procedures involved multiple people from two laboratories as well as off-campus phlebotomists. Hence, they are presented below in enumerated formats for purposes of clarity and later replication, in overview, followed by a detailed description.

Step-Wise Protocol (Overview).

I. Participants were asked to verify that they signed the consent form. The investigator reviewed the protocol and participants were invited to ask any remaining questions they may still have had at that point.

II. The phlebotomists conducted the pretest blood draws, two participants at a time.

III. Blood samples were immediately stored in an insulated transport box packed with crushed ice and transported to the biology lab where they were cold centrifuged (4 °C) and stored. Samples were vortexed at 1500 rpm for 12 minutes and plasma was recovered and stored in a -80 °C freezer. ELISA assay kits were used to analyze oxytocin, vasopressin, dopamine, and cortisol from the blood samples. Briefly, 100 ml of sample were placed in a 96 well plate coated with primary antibodies to capture each respective peptide. The sample was placed as a whole serum, except for cortisol, in which a steroid displacement reagent was used. Following incubation of samples, several washes with the wash buffer provided by the kit were performed, and incubation with secondary antibody was achieved as specified by the kit. Substrates provided by the kits were used to make color changes in the wells. Absorbance was read with a microplate reader set to 405 nm for oxytocin and cortisol, and 450 nm for dopamine and vasopressin.

IV. Participants first engaged in an instrumental music improvisation structured tonally using Phrygian mode such that all pitches were relatively consonant with each other and there were no perceptible "wrong notes" (Roth, 2014). Participants were given instructions prior to the start of the musical experience. First, participants were directed to take 30–60 s to explore their instrument and all of its various sonorous qualities, its responsiveness, and their ability to manipulate the instrument. Once that was completed, participants were instructed to improvise using the following form: A, B-A, C-A, D-A, E-A, where "A" was the group playing in unison and letters B, C, D, and E denote individual improvisations. After four measures of synchronous group playing (A), individuals (B, C, D, and E) played a solo comprising two phrases of two measures each. The whole group responded by imitat-

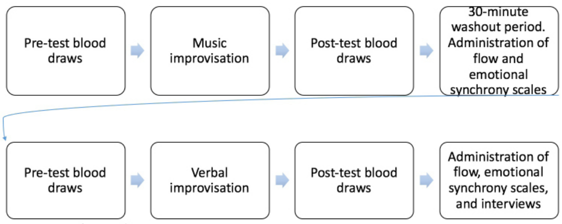

FIGURE 1.
Stepwise flow of protocol.

ing some aspect (e.g., rhythm, tonal contour, etc.) of each individual's second phrase. In this structure, the music systematically alternates between individual improvisations and synchronous performance in a way that conveys empathy, that individual improvisations have been heard, validated, and endorsed (Bruscia, 1987; Gardstrom, 2007).

V. When music tasks were completed, the phlebotomists conducted post-test blood draws in the same room where pretest draws occurred and blood samples were again transported to the biology lab where they were centrifuged and stored as described above.

VI. A 30 min washout period took place to allow a return toward baseline levels of neurohormones.

VII. Following the washout period, steps II–V were conducted for the verbal condition. The verbal condition consisted of a process that more resembled a group discussion. Participants were instructed to individually improvise a short verbal phrase while other participants listened. As an individual's verbal improvisation came to conclusion, another participant gave some indication that they wanted to respond by physically gesturing (e.g., raising their hand, pointing to themselves, nodding their head, etc.) or simply began to talk. They responded to the previous participant's improvisation by first incorporating some aspect and reflecting the emotional tenor of that person's improvisation to demonstrate empathy. This was followed by a period of improvisation where the individual introduced their own idea(s) and the process continued.

VIII. Following the verbal improvisation period, each participant had their blood drawn again, utilizing the same phlebotomy, transport, and storage procedures as described previously.

IX. After the completion of the final blood draw, the phlebotomists ensured the well-being of the participants after which, they were free to leave.

RESULTS

Data for the two primary outcome categories, feasibility and scientific effects, are presented below. Data and related analyses for both outcome categories are reported based on recommendations and formatting guidelines initially developed by Thabane et al. (2010) and further described by Eldridge et al. (2016), LaGasse (2013), and Thabane et al. (2016). Also, the *Reporting Guidelines for Music-Based Interventions* developed by Robb et al. (2011) provided further considerations in the presentation of the following results and discussion.

Feasability Outcomes

Enrollment took place over a period of two weeks. A total of 39 expressions of interest were received and responded to, and enrollment was closed when the target sample of two females and two males in each group (nonmusicians and musicians) consented to participation in the study. All eight participants who provided consent to participate completed the study. Each participant, through their comments and actions, demonstrated that they understood how to complete each component of the protocol and all eight participants completed all of the interventions, blood draws, surveys, and interviews, for a total completion rate of 100%. There were no adverse events reported by any of the participants, although one participant did require more than one needle poke for three of the four blood draws. That participant was poked seven times to obtain the four blood samples. Total time of completion was 2 h 23 min for nonmusicians and 2 h 2 min for musicians. Data collection began at 4 PM for nonmusicians and 5 PM for musicians, so any observed differences in biochemistry between the two groups would not likely be attributable to time of day. The study design allowed for all planned comparisons including nonmusicians versus. musicians, females versus males, and pre-to-post-test changes in cortisol, dopamine, oxytocin, and vasopressin. All aspects of the music technology worked as planned, including the desktop computer and software, amplifier, and MalletKat instruments (Alternate Mode, n.d.). The kits used to obtain blood samples by the phlebotomists were used as planned. Materials used to transport blood samples from the location of data collection to the laboratory for analyses were adequate to the task. Labeling of blood samples at the location of data collection was clear to lab members as they prepared the samples for further analyses.

Neurochemistry Outcomes

A series of t tests were used to analyze between groups (independent t test) and within groups (dependent t test) volumetric change comparisons. They included pretest to post-test changes in all neurohormones comparing nonmusicians (n = 4) to musicians (n = 4) between and within music and verbal conditions, comparing females (n = 4) to males (n = 4) between and within music and verbal conditions, and comparing music improvisation (n = 8) to verbal improvisation (n = 8) regardless of musical background and sex. Within-group analyses examined pretest to post-test hormonal changes for each category of participant, that is, nonmusicians, musicians, females, and males. In this case, p values were used as descriptive and not as expressions of population differences. Where they met the traditional αthreshold of .05, they were reported according to standard guidelines as presented in Field (2017).

Between-Groups Comparisons

On average, there were no statistically significant differences found in pre to post-test change in volumes of any of the neurohormones examined between nonmusicians and musicians for either the music or verbal conditions. However, on average, the change in pre- to post-test volume of cortisol was greater for males (M = −.033, SE = .019) than it was for females (M = .025, SE = .013) following music improvisation regardless of music background. This difference, .058, 95% CI [.003, .114] was significant, $t(6) = 2.56$, $p = .04$ (uncorrected). All other changes in neurohormone volume from pre- to post-test examined between females and males were statistically nonsignificant.

Within-Group Comparisons

MALES

On average, pre- to-post-test concentrations of cortisol in males decreased after music improvisation (M = −.033, SE = .019) and increased after verbal improvisation (M = .026, SE = .021). This difference, .059, 95% CI [.092, .026] was significant, $t(3) = 5.68$, $p = .01$ (uncorrected).

NONMUSICIANS

On average, concentrations of vasopressin increased for nonmusicians from pre- (M = .183, SE = .020) to post-test (M = .229, SE = .015) following verbal improvisation. This difference, .045, 95% CI [.004, .086] was significant, $t(3) = 3.52$, $p = .04$ (uncorrected). All other within-group changes in volumes of neurohormones, including those for females and musicians, were statistically nonsignificant.

DISCUSSION

The current study aimed to assess the feasibility of the study design and explore any neurohormonal changes that may have resulted from engaging in interactive improvisatory behavior. To the author's knowledge, it may be the first to attempt to examine the underlying neurochemistry of live improvisational music making and spontaneous verbal dialogue among musicians and nonmusicians. Previous studies examining changes in neurohormones as a result of interacting with music were based on participants passively listening to music (Ferreri et al., 2019; Menon & Levitin, 2005; Salimpoor et al., 2011, 2013) or with rote music making (Bullack et al., 2018; Fancourt, Williamon, et al., 2016; Keeler et al., 2015; Pearce et al., 2015; Schladt et al., 2017). Given the interactive nature of most applications of improvisation for therapeutic purposes, the differentiation between improvisational and rote music making may be useful when selecting the types of music experiences to be employed in therapeutic contexts for people with disorders impacting socioemotional functioning. Comparing improvisational music making to verbal dialogue also may provide a biological basis on which to make decisions about types of treatment across groups of musicians and nonmusicians. Prior to the onset of the study, it was unknown whether participants would be able to complete the full protocol, primarily due to any discomfort or anxiety created by the blood draws. This aspect of the study has implications for a fully-scaled version to be carried out in the future.

Recruitment, Retention, and Design Considerations for a Larger Study

As LaGasse (2013) pointed out, when conducting feasibility and pilot research, primary areas to be considered for successful implementation of the study include assessment of the ability to recruit, consent, and retain participants; random assignment process; implementation of the intervention; and scientific outcomes. As mentioned earlier, recruitment was not an issue as 39 individuals who met the inclusion criteria expressed interest in participating. The retention rate for this study was 100%.

In a fully powered study, stratified block randomization would be the most useful design to ensure equal-sized blocks that also account for covariates (Suresh, 2011). Also, counterbalancing the musical and verbal interventions would be important to mitigate any learning or comfort effects that might occur as a result of intervention order in a scaled-up study.

For the most part, the intervention was implemented as conceptualized. Based on their behaviors, comments, and questions, all participants appeared to understand the directions and performed study tasks as instructed. Participants in the nonmusician group were able to quickly grasp the musical task and reported that they better understood what was being asked of them and felt more comfortable over the duration of the improvisation. Musicians reported understanding the task immediately, but also reported becoming more comfortable with playing instruments that were not their applied instrument over the duration of the improvisation. More details regarding participant comments are reported in a separate mixed methods study. The duration of time for each component of the protocol was not measured but may need to be considered when bringing the study to scale. External events may also need to be considered during scheduling of data collection to limit participant fatigue, as data collection for the group of musicians in this study took place on the last day of their final exams.

Data collection for each group lasted slightly longer than estimated, as indicated earlier, and although the duration of each portion of the protocol was not calculated, it is possible that this was due to the collection of blood taking longer than originally planned. Participants were asked before and after each blood-collection period if they felt well enough to continue and each participant responded positively, every time they were asked. The space that was used worked as planned. However, both spaces have been reappropriated to other divisions at the university and new locations will need to be explored to bring the study to full-scale.

All equipment including the musical instruments, amplifier, computer hardware and software, ELISA kits, microplate reader, centrifuge, -80 ˚C chest freezer, other materials from the biology laboratory all were utilized and functioned as planned. Materials supplied by the WMU Environmental Health and Safety Department were obtained through that office as precautionary measures and, fortunately, they were not necessary, as no adverse events occurred.

As mentioned earlier, one participant required a total of seven pokes to obtain four blood samples. After each failed attempt, the phlebotomist asked this participant if she was willing to continue, and after providing consent to do so, the phlebotomist proceeded to obtain the blood sample. It does not seem unreasonable to wonder whether the potentially mildly stressful experience of enduring multiple blood draws in a short period of time could influence all or some of the neurohormones examined in this study. It remains uncertain whether thirty minutes was sufficient to allow these specific neurohormones to return toward baseline. In part, this could be attributed to the need for a longer period of time for washout. However, there also does not appear to be a widely agreed upon standard of when the return to baseline is achieved. When bringing this study to scale, it may be beneficial to increase the washout period to sixty minutes. Relatedly, although it was hypothesized that the use of blood samples would be the best option to reveal changes in neurochemical activity as a result of study interventions, other researchers have demonstrated that saliva may yield similar results (Fancourt, Perkins, Ascenso, Carvalho, et al., 2016; Fancourt, Williamon, et al., 2016; Schladt et al., 2017; Yuhi et al., 2017) and is less invasive than drawing blood. Given this, use of saliva should be considered when bringing the study to scale to increase the likelihood of recruiting a sufficient number of participants for an adequately powered study.

Neurochemistry Outcomes

The primary purpose of this study was to determine if the design and interventions would be sufficient to yield observable changes in neurohormone activity that could then be used to design a full-scale randomized controlled trial. One statistically significant outcome was that the pre-to-post-test change in cortisol was greater for all males than it was for all females as a result of music improvisation. Of related interest is that the change in cortisol after the music condition was directionally divergent between males and females, with cortisol decreasing for males and increasing for females. In a sufficiently powered study, this could be interpreted a number of ways, including, perhaps, that males became somewhat less stressed whereas females became somewhat more stressed as a result of music improvisation (Brugués, 2011).

Two other statistically significant changes in pre-to-post-test measures were also observed. The first included a difference in cortisol production in all males between music and verbal conditions, where cortisol decreased after the music condition and increased following the verbal condition. Inferences cannot be drawn from such a small sample, but in a sufficiently powered study, one potential interpretation might indicate that compared to interacting musically, males experienced greater stress as a result of interacting verbally (Brugués, 2011; Buck, 1977, 1984; Chaplin, 2015; Levenson et al., 1994).

The second change included a statistically significant pre- to-post-test increase in the production of AVP in nonmusicians following the verbal improvisation. Inferences regarding AVP by itself are challenging (Insel, 2010), as it is thought to interact with OT to mediate socioemotional behavior (Insel, 2010; Johnson & Young, 2017; Meyer-Lindenberg et al., 2011). As mentioned in the review of literature, one function of AVP that has been observed with potential relevance to this outcome is that changes in AVP appear to underlie responses to facial expression (Thompson et al., 2006). This may be relevant here as the significant change in AVP was observed after the verbal condition, where participants were looking directly at each other during their discussion, as opposed to the music condition, where participants were mostly looking downward at their instruments. From that same study (Thompson et al., 2006), ratings of friendliness differed by gender, where the findings demonstrated that men reacted negatively to the faces of unfamiliar men but women reacted positively to the faces of unfamiliar women. No such gender differences were detected in this small pilot study. However, it seems worth noting that nonmusician participants were unfamiliar with each other whereas, by virtue of the inclusion criteria, all participants in the musician group knew each other as they were enrolled in the same university degree program (and they indicated their familiarity verbally as well). A full-scale version of this study should account for familiarity among participants during the assignment stage of the experiment and could include participants who both know and do not know each other. This, of course, has clinical implications as most often, patients being treated in groups with either music or verbal interventions have not met each other prior to the onset of therapy.

A full-scale version of the study should also consider whether the use of additional health-related biomarkers (as described by Fancourt et al., 2014; Fancourt, Perkins, Ascenso, Atkins, et al., 2016; Fancourt, Perkins, Ascenso, Carvalho, et al., 2016; and Fancourt, Williamson, et al., 2016) would be useful in improvisational experiences where inflammation and functioning of the immune system were positively impacted by engagement in rote music experiences. This could be particularly important for various clinical populations.

CONCLUSION

The current investigation provided promising results regarding the ability of the study design and procedures to yield useful information when bringing the study to scale with a sufficiently powered sample. Participants were able to understand and complete the protocol and interventions were robust enough to create observable change in neurochemistry. Further considerations include the use of counterbalancing the order of interventions, familiarity among participants, the use of saliva rather than blood, and the use of additional biomarkers.

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DATA AVAILABILITY

We commit to making our data available for secondary analysis upon reasonable request.

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