Dear Reader,

We are excited to present to you the sixth annual volume of JOURney, the University of North Carolina at Chapel Hill’s first interdisciplinary Journal of Undergraduate Research!

JOURney started as an idea of founder Gabi Stein to create a journal that would showcase the outstanding, diverse range of student research done by UNC-Chapel Hill undergraduates. With the support of the Office of Undergraduate Research, JOURney became an official publication, allowing students a place to publish SURF projects, partial and full honors theses, and independent research.

This year, JOURney has continued to expand, gaining many successes along the way with the receipt of the most-ever number of submissions. With all the excellent work submitted, we are able to exhibit 9 original pieces of work here that explore interesting, topical, and complex areas of research. We congratulate the student authors on all their hard work put into researching and publishing their work!

We are so thankful of everyone who has helped JOURney continue to meet its mission of celebrating and supporting the research conducted early in students’ academic careers. We would like to thank the Office for Undergraduate Research, which has provided JOURney unwavering support since its inception. We would also like to thank our entire editorial board and publicity team, who have spent many dedicated hours into making this edition. As the current Co-Editor-In-Chiefs, we have enjoyed helping JOURney expand as an organization.

We leave you here to explore the work presented in this journal. We hope you will enjoy the knowledge collectively presented to you by the students of UNC-Chapel Hill.

Sincerely,

Mili Dave & Vanya Bhat
2021-2022 JOURney Co-Editor-in-Chiefs
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Machine Learning Applications in School Psychology: A Comparison of Supervised Learning Algorithms for Predicting Adolescent Aggression and Examining Predictive Factors of Aggression

by Adanya Johnson, Alexis Cameron, Keerthi Narasimhan, Taylor Lewis & Alekhya Majety

This paper is based on data from Morgan-Lopez and colleagues’ school based mental health intervention in Charlotte-Mecklenburg County Schools (2020). We sought to predict adolescent aggression levels to acknowledge and analyze the root causes of youth violence and guide intervention and prevention steps for educators, administrators, and mental health professionals. We tested how well a student’s level of aggression can be predicted by assessing their sense of belongingness, quality of teacher-student relationships, degree of perceived racial discrimination, and life outlook. This study tests the effectiveness of random forests and logistic regression algorithms in successfully predicting aggression levels in middle school students. Overall, both algorithms had similar accuracy rates. The random forest algorithm performed better when predicting low levels of aggression in students. The logistic regression had a better performance when predicting high aggression levels. Machine learning algorithms have potential for identifying factors that can be predictors of aggression levels, which can allow for the appropriate allocation of resources for “high-risk” students. The application of this type of model has important ethical
implications for high-aggression students and students that come from marginalized groups. Rather than falsely labeling high risk students and failing to identify aggressive students, we advise that school professionals apply this machine learning algorithm responsibly to prevent the harm of vulnerable populations.

Key words: [machine learning, risk assessment, school-based mental health, aggression, middle school]

INTRODUCTION

Middle school is a formative time for many children where they are experiencing significant life changes. They are transitioning to a new school, taking on greater responsibilities inside and outside of the classroom, and going through puberty. These physical and social changes can be overwhelming and challenging for adolescents to go through alone. 75% of adolescents do not receive the proper mental health services, and a potential explanation for this is that those at risk are not being accurately screened for mental health issues (The Children’s Society, 2021). Most current school-based treatment programs do not focus on aggression assessment and identification, leaving out at-risk students as a result. This study will utilize supervised machine learning algorithms to predict aggression levels in middle school students by examining a student’s sense of school belongingness, teacher-student relationships, degree of perceived racial discrimination, and level of hopelessness.

LITERATURE REVIEW

Researchers in school and clinical psychology have implemented school-based mental health (SBMH) programs aimed at improving students’ well-being, identifying students at risk, and prevention (Morgan-Lopez et al. 2020). These programs focus on externalizing behaviors, specifically aggression.

Assessing Risk for Aggressive Behavior

Paper Assessments. There have been numerous programs studying the effectiveness of preventing and reducing aggressive behavior at school-wide level. However, more research on assessing and detecting at-risk students and identifying factors for school-based aggression is needed. The SAVRY identified protective and risk factors of aggression. The internal validity showed a consistency of 0.82 for community samples. Despite this, the reliability of this tool is low, as the SAVRY is rooted in structured professional judgment rather than data-driven statistics.

Automation and Machine Learning. Most of the current risk assessments are paper-based and require clinical input or structured professional judgment. While initial results were promising, these methods can be slow, and accurate screening rates have lowered to less than 50% (Barzam et al., 2018). Machine learning has the potential to alleviate some of these issues, however few studies exist on using the technique to automate risk assessments in schools. Given the lack of studies on the application of machine learning on risk assessment, this study hopes to provide additional knowledge on the potential of automated risk assessment in the school setting.

Teacher-Student Relationships

A positive teacher-student relationship is evidenced by teachers’ low report of conflict, emotional connection, and support they provide to the student. Research has shown that healthy teacher-student relationships are critical for positive development in students, and that high-quality relationships predict lower aggression levels in adolescents and subsequent delinquent behavior (Rimm-Kaufman, n.d.; Hughes & Cavell, 2010; Hamre & Pianta, 2001; Obsuth et al., 2021).

Perceived Racial Discrimination

Perceived racial discrimination refers to minority perception of unfair treatment based on racial prejudice or racism (Noh et al., 1999). Externalizing problem behavior in minority students is likely to manifest as a response to experiencing racial discrimination (Fisher et al., 2000; Rosenbloom & Way, 2004). Moreover, perceived racial discrimination results in increased negative emotions, which eventually led to aggressive behavior in adolescents (Xiong et al., 2021).
Outlook on Life

In the case of adolescents, when exposed to stressors they deem uncontrollable, they are likely to experience hopelessness and use apathetic or avoidant coping behaviors. In addition to apathetic coping behaviors, research suggests that feelings of hopelessness can also manifest as aggressive behavior in adolescents. Hopelessness has been shown to predict whether adolescents will become involved in high-risk and violent behaviors (Landis, 2007; Duke et al., 2011).

Sense of School Belonging

School belonging is defined as students' feeling of acceptance, respect, inclusion, and support in a classroom or academic environment (Goodenow, 1993). Reported feelings of connection and adequate support from the school were correlated with decreased aggression and violent youth behaviors in middle and high school students (Duggins et al., 2016; Valido et al., 2021; Fleming et al., 2010). The results of these studies provide evidence that poor sense of school belonging in students is related to higher levels of aggressive behavior in school.

RESEARCH GOAL

While there is a plethora of research on implementing SBMH services, more research is needed on identifying school risk factors and identification. To improve risk assessment in schools, we proposed using supervised machine learning to predict aggression levels in children. Current literature has demonstrated a connection between adolescents' level of aggression, a sense of school belongingness, perceived racial discrimination, quality of teacher-student relationships, and their overall outlook on life. The objectives of this study are:

- Use data on students' quality of relationships with teachers, positive and negative outlook on life, degree of perceived racial discrimination, and sense of school belongingness to predict aggression levels
- Identify the most important predictors of aggression in middle school students
- Compare random forest and logistic regression as machine learning classification algorithms
- Examine the relationship between students' quality of relationships with teachers, positive and negative outlook on life, degree of perceived racial discrimination, sense of school belongingness, and aggression levels.

METHODS

RTI's SBMH Study

This study expands upon the study on school safety and SBMH services conducted by RTI International. RTI International assessed interventions that targeted and treated selected individuals with mental health issues and then evaluated the subsequent impact on the entire school population's experience of aggression and victimization (Ballard et al. 2014).

Dataset

The dataset for this study was made publicly available by RTI International. The original study contained cross-sectional survey data from students and staff at four distinct time points across three school years as well as implementation data collected from mental health providers. The variables of interests for this study are sense of school belongingness, the quality of teacher-student relationships, degree of perceived racial discrimination, outlook on life, and aggression.

Random Forest

The first algorithm used to predict adolescents' aggression levels and assess the strongest predictors is random forest. Random forest (RF) is an ensemble machine learning algorithm often used for classification and regression problems. RF combines bagging and random sampling of predictors to create an assembly of decision trees (Fawagreh et al., 2014). With bagging, the n datasets are created by resampling and replacing the original dataset. For each of the n bootstrapped datasets, a decision tree is created. The predicted value or classification is calculated for each tree, and the average predicted value or majority-vote classification is calculated. To improve prediction, RF utilizes random input selection. Each decision tree is formed by, at each split or node, randomly selecting n variables (Breiman, 2001).

RF is one of the most commonly used algorithms in data science and other quantitative fields due to its simplistic nature and accurate predictions. It can handle outliers and noise in the dataset, performs better than other machine learning methods such as bagging and classification and regression tree (CART), and provides internal estimates of variable importance, strength, error, and correlation (Breiman, 2001).

Procedure

All statistical analyses were carried out in R and
To carry out the RF algorithm, the randomForest R-package was used. 500 trees were grown in 500 bootstrapped datasets to produce final predictions. At each split, two predictors were randomly sampled. Variable importance was calculated and plotted to determine the most important predictors of aggression. To carry out logistic regression, the glm function from base R was used. A multiple regression was conducted to assess the predictive strength of each independent variable. To assess the strength and direction of each predictor in relation to aggression, correlations were run. These analyses supplement our results from machine learning models.

RESULTS

Machine Learning

The data was divided into a training set, where the models were built, and a testing dataset, where the model performance was evaluated. The training dataset consisted of survey data from 2016 and 2019 (N = 6492). The testing dataset consisted of survey data from 2017 and 2018 (N = 6234). Prior to building the model, the training dataset was balanced via up-sampling. The model was evaluated using unbalanced data to mimic real-life performance.

Random Forest Model

Table 1 represents the model performance of the RF model. Overall, the model correctly predicted students as high or low risk for aggression or low aggression 65% of the time. The miscalculation rate is .35. The sensitivity is .44, indicating the model correctly identifies students who have high aggression levels 44% of the time. The specificity is .66, meaning the model correctly identifies students who have low aggression levels 66% of the time.

Variable importance for the model was calculated and plotted (Figure 1). In order, the most important variable is school belonging, followed by teacher-student relationships, life outlook, and perceived racial discrimination.

Logistic Regression Model

A logistic regression was run to determine the probability of belonging to low or high aggression. Table 2 represents the model performance of the logistic regression model. The model correctly predicted students’ aggression levels 62% of the time. The miscalculation rate is .38. The sensitivity is .57, meaning the model correctly identifies students with high aggression levels 57% of the time. The specificity is .62. The model correctly identifies students with low aggression levels 62% of the time.

Inferential Statistics

Logistic Regression

Logistic regression analysis was used to examine the relationship between school belonging, teacher-student relationship, perceived racial discrimination, and life outlook on the probability of a student displaying low or high aggression. We found, while holding all else constant, the probability of displaying high aggression increased when students experienced racial discrimination \( [B = 0.39, p < .001, OR = 1.48 (95\% CI: 1.42,1.54)] \). While holding school belonging, racial discrimination, and life outlook constant, the probability of a student displaying high aggression decreased as their relationships with teachers improved \( [B = –0.39, p < .001, OR = 0.68 (95\% CI: 0.65,0.72)] \). The probability of displaying high aggression slightly decreased as students’ life outlook increased \( [B = -0.08, p < .001, OR = 0.92 (95\% CI: 0.89,0.96)] \). School belonging was not a significant predictor of whether a student displayed low aggression or high aggression.

Multiple Regression

A multiple regression was run to assess how well teacher-student relationships, outlook on life, perceived racial discrimination, and school belonging predicted student-rated aggression levels.
DISCUSSION

This study compared RF and logistic regression as machine learning classification algorithms for predicting adolescent aggression and examined the relationship between teacher-student relationships, perceived racial discrimination, outlook on life, school belonging, and aggression.

Overall, the (RF) model and the logistic regression model performed similarly. The (RF) model correctly identified students’ aggression level 65% of the time, while the logistic regression correctly identified students’ aggression level 62% of the time. (RF) was slightly better at predicting students who exhibit low levels of aggression. The logistic regression model outperformed the (RF) model for predicting students with high aggression. The variable importance measures indicated school belonging is the greatest contributor to a student’s aggression levels, followed by teacher-student relationships, life outlook, and perceived racial discrimination.

The logistic regression results indicated teacher-student relationships, outlook on life, and perceived racial discrimination significantly changed the probability of having high aggression or low aggression. Higher rated teacher-student relationships and positive outlook on life decreased the probability of a student exhibiting high aggression. More frequent experiences with racial discrimination increase the probability of a student displaying high aggression.

ETHICS

During the process of building the machine learning algorithms, we considered the potential consequences of having a poor sensitivity or a poor specificity. Imagine a middle school implements the logistic regression algorithm for detecting aggressive behavioral risk in students. If a student is incorrectly predicted to be low risk for aggressive behavior and begins exhibiting aggressive and other externalizing behaviors, their teachers and school administration will likely identify it and provide the child with the proper mental health service. However, if the undetected child is a student of color, there’s a higher likelihood that their mental health needs go unaddressed. Black, Latino, and Asian Americans are less likely to seek mental health services and more likely to experience higher levels of stigma compared to White Americans (Alvidrez et al., 2008; Cabassa, L.J., 2007; Nishi, 2021). Conversely, it is important to examine potential repercussions if a student is incorrectly flagged as high risk for aggressive behavior. While they may originate with well-meaning intentions, the labels themselves can cause harm. Labeling theory states youth stopped or arrested are subsequently excluded from typical activities, leading them to adopt a deviant identity and engage in delinquent behaviors (Wiley et al. 2013).

While machine learning has the potential to identify students for individualized care, its use raises ethical questions that must be addressed. Machine learning in schools has the ability to significantly aid in school and clinical psychology settings, nonetheless the ethical and societal implications should not be ignored. Inaccurate algorithms can result in the mental health of students going undetected or contribute to the stigmatization of mental health and behavioral issues. Additionally, if abused, machine learning could perpetuate inequities and oppression that exist in society. Researchers, school leaders, teachers, and clinicians have a duty to build and apply machine learning responsibly to maximize students’ benefit.

DIRECTIONS FOR FUTURE RESEARCH

This research adds to a growing collection of research exploring the implementation of SBMH Programs. This study explores the potential application of machine learning in school environments, however more research is needed on the ethics and implications of such technology. Future studies could potentially answer these concerns. For instance, researchers could conduct a longitudinal study following students who receive a SBMH intervention after being identified as high-risk for aggression; the data collected from such a study could be compared with control groups to evaluate the impact of the intervention. Additionally, that data could be compared with historical data to see whether the intervention was effective at reducing the overall population of aggressive students over
time. Studies such as this could not only expand the potential applications of our machine learning findings, but they could also inform researchers with guidelines for similar models that may be created in the future, and for diverse applications of our findings to real school settings.

LIMITATIONS

This study used cross-sectional data which is difficult to examine for temporal dynamics and thus determine whether the predictor variables cause aggression or if aggression leads to poorer outcomes in the predictor variables. Additionally, each variable has a unique scale (i.e. Likert scales, number of categories), reducing reliability of variable importance measures. Thus, inflation can occur depending on how important certain variables are in our prediction process compared to others (Strobl, 2007). For example, school belonging is the highest variable of importance value, yet it was not significant in the logistic regression or multiple regression model.

CONCLUSION

This study compared supervised machine learning algorithms (RF and logistic regression) for the prediction of adolescent aggression. It also sought to examine the relationship between school belonging, quality of teacher-student relationships, perceived racial discrimination, outlook on life, and aggressive behavior. RF performed better for predicting low aggression, while logistic regression had a higher accuracy for predicting high aggression. Additionally, our study supports previous findings that outlook on life, perceived racial discrimination, and teacher-student relationships predict aggressive behavior in students. However, school belonging did not significantly predict aggression. When implementing machine learning in schools, ethical and societal considerations for high-aggression students, students of color, and other marginalized groups must be taken into account. We suggest future research expand predictive models to include additional variables as well as utilize longitudinal data to examine temporal dynamics and long-term outcomes of machine learning use.
The Effect of COVID-19 on the Mental Health of Resident and Fellow Physicians: A Cross-Sectional Study
by Essie Acquah

The Coronavirus Disease 2019 (COVID-19) outbreak has made the lives of healthcare workers increasingly difficult. Healthcare workers have had to adjust to the sudden influx of patients in critical conditions, shortages in personal protective equipment (PPE), among other challenges. While medical trainees have been affected with major disruptions to their education, they remain underrepresented in the literature about the impacts of the pandemic on physicians and their mental health. Our study aims to assess how the COVID-19 pandemic has impacted medical trainees’ education and determine which factors are associated with their mental health. From March to May of 2021, an electronic survey was disseminated to trainees in medical institutions across North Carolina. The majority of trainees (55.3%) stated COVID-19 had somewhat worsened their training experience. When examining overall wellbeing, 60.5% of trainees reported that the pandemic significantly worsened their social lives. Where possible, medical training programs should implement the use of mental health resources to support residents in times of high stress.

Keywords: COVID-19; Mental Health; Stress, Psychological; Health Surveys

INTRODUCTION

The outbreak of Coronavirus Disease 2019 (COVID-19) has disrupted our world. Policies such as government mandated lockdowns, post-exposure quarantine, implementation of compulsory mask use in public, and social distancing guidelines have significantly impacted society. The pandemic has caused increases in societal stress and anxiety as economic uncertainties prevail, the threat of contracting the COVID-19 virus looms, and morbidity due to COVID-19 continues (Salamah et al., 2020). The pandemic also changed the world of education, including that of residents training to become physicians. Residents experienced disruptions to their learning throughout the pandemic, including transitions to virtual education and patient care. In pre-pandemic conditions, trainees typically spent 40 to 80 hours a week interacting with and treating patients. As the pandemic forced changes to education and a transition to telehealth care, trainees had reduced in-person clinical opportunities, surgical trainees performed fewer elective surgeries, and most trainees cared for a high volume of COVID-19 patients (Rana et al., 2020). Burnout, previously a widely discussed topic in medical careers, has again come to the forefront of concern during the pandemic (Chew et al., 2020).
The sudden onset of multiple life adjustments has the potential to increase stress and anxiety among trainees. Adjusting to new personal protective equipment (PPE) donning and doffing procedures and the increase of critically ill patients can induce stress in the work environment (Barik et al., 2020). Outside of work, the concern of possibly infecting family members and post-exposure quarantine periods can have negative impacts on overall mental health (Chew et al., 2020). Our research aims to assess the effects of the COVID-19 pandemic on the mental health of resident physicians in North Carolina.

METHODS

Study Design

This study is a cross-sectional study of resident physicians and fellows in North Carolina. An electronic survey was developed by the researchers and distributed by the Designated Institutional Official (DIO) at each hospital to the trainees of their institutions. The anonymous survey data were captured using Qualtrics software (Qualtrics, Provo, UT). This study was reviewed and determined to be exempt by the University of North Carolina's Institutional Review Board.

The 72-item survey included closed-ended questions regarding demographics, trainee reported COVID-19 patient encounters, work environment conditions, and mental health. A free response section was available to allow participants to write about their experiences in their own words.

Trainees were asked to identify their program specialty. Responses were condensed into nine subcategories: internal medicine; family medicine; pediatrics; emergency medicine; anesthesiology; obstetrics and gynecology (OB/GYN); general surgery; surgery subspecialties; and other.

To assess overall mental health, the Depression, Anxiety and Stress Scale-21 (DASS-21) (Lovibond, S.H. & Lovibond, P.F., 1995) was used. Validity and reliability of this 21-item scale have been previously established (Coker et al., 2018). The total and three subscales (i.e., stress, anxiety, depression) DASS-21 scores were calculated. Due to the limited number of responses, participants were categorized as "Normal", "Mild/Moderate", or "Severe/Extremely Severe" for each subcategory and Total DASS-21 score. Anxiety scores were labeled as Normal (0-7), Mild/Moderate (8-14), and Severe/Extremely Severe (15+). Depression scores were labeled as Normal (0-9), Mild/Moderate (10-20), Severe/Extremely Severe (21+). Stress scores were labeled as Normal (0-14), Mild/Moderate (15-25), and Severe/Extremely Severe (26+).

Survey Pretesting

Prior to dissemination, the survey was pretested with a group of 12 residents. All residents were employed at a single academic medical institution and represented nine different residency programs. Residents were asked to complete the survey and provide feedback. Feedback allowed for revision of the questions to provide participants with additional context, the questions were revised using pilot feedback prior to formal survey launch in March 2021.

Data Analysis

Trainee responses to closed-ended demographic and experiential questions were assessed using descriptive statistics. Through literature review and team discussion, the research team identified sixteen demographic and experiential variables potentially associated with mental health. The statistical significance (p≤0.05) between total DASS-21 and the priorly selected variables were assessed using Spearman's Rank Correlation for continuous variables, Wilcoxon Rank Sum Test for dichotomous variables, and Analysis of Variance for polytomous variables. Variables exhibiting a statistically significant relationship with total DASS-21 were entered into a forced linear regression model; insignificant variables within the model were dropped to produce the final model. All quantitative descriptive and inferential analyses were conducted using R (R Core Team, 2021). Qualitative data from open-ended questions are presented for context.

RESULTS

The survey was opened 184 times. Participant responses were excluded if <33% of the survey was completed (n=23). One survey response was excluded because it was completed outside of the response timeframe (i.e., March to May 2021). In total, 160 responses were analyzed.

Participant Demographics

Approximately 58.1% of participants identified as female. The majority of participants identified as White (79.2%) and non-Hispanic/Latinx (92.5%). Respondents' ages ranged from 26 to 44 years (mean=31 years). Though there was a range of 1-7 years of current residency training to-date, most participants were within their first three years of residency (70.0%) (Table 1).

Nearly all (98.7%) trainees reported they received the COVID-19 vaccine. Out of 160 participants, 19 reported they had a high-risk health condition for
COVID-19, and 21 people reported having a family member that was high risk (Table 1).

**Effect of COVID-19 on Trainees’ Personal and Professional Life**

To determine the effect of COVID-19 on their mental health, participants were asked to rank how the pandemic impacted various parts of their life (Table 2). When asked about how the availability of the vaccine affected overall stress, 51.6% of trainees reported that it significantly decreased their stress levels. When asked to reflect on how the pandemic has affected overall residency training, 55.3% of trainees stated COVID-19 had somewhat worsened their experience. Additionally, 60.5% of participants believed the pandemic significantly worsened their social lives.

![Table 1: Participant Demographics](image)

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<tr>
<th>Age (years)</th>
<th>Mean (Range)</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>0</td>
<td>23.4 (37)</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>18.7 (26)</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>17.7 (28)</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>5.7 (9)</td>
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<td>4+</td>
<td>5.1 (8)</td>
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<td>0</td>
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</tr>
<tr>
<td>1</td>
<td>11.2 (18)</td>
</tr>
<tr>
<td>2</td>
<td>6.9 (11)</td>
</tr>
<tr>
<td>3</td>
<td>2.5 (4)</td>
</tr>
<tr>
<td>4+</td>
<td>0.6 (1)</td>
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<th>Race</th>
<th>n (%)</th>
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<td>Other/Not Spec</td>
<td>20.6 (33)</td>
</tr>
<tr>
<td>Hispanic/Latin</td>
<td>79.2 (126)</td>
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<th>Year of postgraduate training</th>
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<td>PGY-1</td>
<td>20.0 (32)</td>
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<tr>
<td>PGY-2</td>
<td>20.6 (33)</td>
</tr>
<tr>
<td>PGY-3</td>
<td>29.4 (47)</td>
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<tr>
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<td>12.5 (20)</td>
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<tr>
<td>PGY-5</td>
<td>11.2 (18)</td>
</tr>
<tr>
<td>PGY-6</td>
<td>4.4 (7)</td>
</tr>
<tr>
<td>PGY-7</td>
<td>1.9 (3)</td>
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<th>Training program</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Anesthesiology</td>
<td>4.4 (7)</td>
</tr>
<tr>
<td>Emergency Medicine</td>
<td>11.2 (18)</td>
</tr>
<tr>
<td>Family Medicine</td>
<td>10.0 (16)</td>
</tr>
<tr>
<td>General Surgery</td>
<td>5.6 (9)</td>
</tr>
</tbody>
</table>

- **Fellowship**
  - No: 79.6 (115)
  - Yes: 21.4 (34)

- **Trainee at high-risk for COVID-19**
  - Yes: 11.9 (19)
  - No: 88.1 (141)

- **Family member at high-risk for COVID-19**
  - Yes: 13.1 (21)
  - No: 86.9 (139)

- **Vaccinated for COVID-19**
  - Yes: 98.7 (152)
  - No: 0.6 (1)

- **Scheduled**
  - Yes: 6.1 (1)

- **Patients seen in-person during COVID-19**
  - 0: 5.2 (8)
  - 1-100: 81.9 (130)
  - 101+: 10.9 (17)

- **Telehealth patients seen during COVID-19**
  - 0: 46.5 (72)
  - 1-100: 52.3 (81)
  - 101+: 1.3 (2)

Based on team discussion and literature review, 16 variables were identified as possibly impacting trainee mental health during the pandemic (Table 3). To determine association with Total DASS-21 score, these variables were assessed as previously described in the Methods section. Of the initial 16 variables identified, 4 were significantly associated with Total DASS-21 score in these initial statistical tests.
Table 4 presents the results of the multiple linear regression. All variables tested against and significantly related (p≤.05) to Total DASS-21 Score were entered into a multiple linear regression model. Two variables remained significantly associated with Total DASS-21 Score, including the trainee’s concern for giving COVID-19 to their family members and whether the trainee had access to enough PPE at work. The original model with four predictors was significant (F12,138=3.934, p=3.293e-5), accounting for ~19% of medical trainee’s Total DASS-21 Score. When the two insignificant independent variables were dropped, the model remained significant (F5,148=4.591, p=6.372e-4), accounting for ~11% of medical trainee’s Total DASS Score. Availability of workplace PPE and trainee’s concern for giving their family COVID-19 were tested for collinearity using Fisher’s Exact Test. Collinearity was not detected between the two independent variables (p=0.274).

To illustrate the results of the final linear regression, Table 5 was developed to highlight how changing PPE availability in the workplace or a trainee’s perceived risk of giving their family COVID-19 can affect a trainee’s mental health. This table indicates the positive association between Total DASS-21 score and concern for giving family COVID-19.
DISCUSSION & LIMITATIONS

The COVID-19 pandemic affected medical trainees' professional experiences. Most participants (55.3%) reported that the pandemic significantly worsened their residency training experience. This experience was also reported by Barik et al. (2020) who found a decrease in outpatient clinical experience and fewer elective subspecialty rotations. One participant described changes to their training since the pandemic by stating:

"I feel this was a lost year, mentorship effectively evaporated in last year of fellowship. Missed out on a year of bonding with co-fellows and department colleagues."

In addition to loss of professional resources, medical trainees may have experienced increased burnout. Physician burnout, or the negative change in emotional and physical capacity to perform as a physician, has been associated with intense workloads and minimal colleague support (West et al., 2018). One participant testified as to the effect of reduced vacation time during the pandemic:

"We were also required to use our very limited PTO (10 days for both vacation or sick leave per year) anytime we were quarantined for testing or out with COVID symptoms. This policy effectively insured residents did not get any vacation time during 2020."

However, not all trainees were equally affected by workplace stress. Among the 2.0% of participants who responded that the pandemic "somewhat improved" their residency training are trainees who felt they benefited from the COVID-19-related training they did receive.

"Residency training has been affected in various ways - on the one hand I've had greater exposure to [Critical Care Management] including vent management, anesthesia management, end of life discussions, etc." The effects of the pandemic extended beyond one's professional training and into one's social life. Most trainees (60.5%) felt the pandemic had significantly worsened their social life. Not having as much time to connect with peers and coworkers may have contributed to social isolation, a phenomenon felt by 57.2% of participants. According to participants, some programs experienced educational budget cuts and collaborative lectures were transitioned to virtual meetings, potentially contributing to increased feelings of social isolation.

The source of medical trainee's stress extended outside of, but remained influenced by, the evolution of the workplace during a pandemic. The pandemic negatively affected 71.1% of trainee's personal lives and 90.5% of trainee's social lives. The stress of COVID-19 on family dynamics and relationships has been established, as evidenced across the world through various infection prevention methods including isolating away from family (Guarino, 2020). One trainee shared their experience of stress as both a physician and a parent:

"For physicians with young children, part of the stress of the pandemic has been arranging childcare for school-age children in online learning platforms. Additionally, the stress of children in daycare with common symptoms...now meant no childcare until Covid testing could be undertaken which sometimes took days to result. All of it without much support from our programs other than vacation time taken away."

While another trainee expressed how they felt a different emotion, anger, when communicating with friends and family:

"I have numerous friends and family that don’t take COVID seriously or don’t get the vaccine, which makes me irrationally angry."

Identifying areas to reduce stress during a pandemic is an important step in improving medical trainee well-being. While total DASS-21 score among medical trainees can be predicted based on their concern for giving COVID-19 to their family and their workplace access to PPE, the factor most amenable to change in the workplace is their access to PPE. From the mathematical formula shown in Table 5, we can predict the change in a trainee's Total DASS-21 score when changing either or both variables. For a trainee who is "not concerned" about transmitting COVID-19 to their family, we can reduce their Total DASS-21 score from 37 to 14 by increasing PPE availability from "sometimes" to "always". For a trainee who is "very concerned" about transmitting COVID-19 to their family, we observed the largest reduction in Total DASS-21 score from "most of the time" (DASS-21=51) to "always" (DASS-21=32) in the provision of PPE. Having inconsistently available PPE at work leads to increased stress. One resident shared their experience with PPE at their institution:

"The first three months of the pandemic (March to May 2020) our institution would not allow us to wear a mask ("it would scare the patients") or bring our own N95 from home to wear ("others don't have access and we won't know who took them from work.")
was stressful and extremely disheartening.”

One limitation of this study is the small sample size. Of the 160 participants who answered the DASS-21 questionnaire, approximately 73.3% of participants were within the “normal” range of DASS-21 subscales. Generally, medical trainees tend to have much higher rates of depression and anxiety compared to the general population (Mouse et al., 2016) so this result may be due to self-selection bias within our sample. Another potential limitation is survey timing; the survey was sent out at a time between the surge in two prominent COVID-19 variants, delta and omicron, which may have affected stress and changed medical trainee’s perceptions as the pandemic evolved.

Ultimately, it is the responsibility of the workplace to ensure medical trainees have access to the tools and resources needed to combat workplace burnout, stress, and exposure to communicable disease during a pandemic. However, the availability of mental health resources for medical professionals should not be limited to the time of an active social crisis such as a pandemic. By ensuring resources are in consistently place, medical trainees can better protect themselves and serve their patients.
Bibliography


Essie Acquah is a first-year student at UNC-Chapel Hill currently majoring in Neuroscience. Essie began her COVID-19 mental health independent research project during her senior year of high school through a mentorship program in partnership with UNC Hospitals under the supervision of Dr. Jane H. Brice, Dr. Maglin Halsey-Nichols, and Ms. Julianne M. Cyr. She has research interests in mental health, neurological disorders, and the effects of selective serotonin reuptake inhibitors (SSRIs). She is currently working as a research assistant in the Social Neuroscience and Health Lab under Dr. Keely Muscatell in the UNC Department of Psychology and Neuroscience.
Inequity in Homeownership: Closing America’s Racial Wealth Gap
by Rohan Tapiawala

This policy review examines the role of the racial homeownership gap in creating racial wealth disparities in the United States. Homeownership is the primary driver of wealth accumulation in the U.S. Obstacles to homeownership have plagued Black populations for centuries, creating vast differences in homeownership between Black and white Americans that have played a key role in widening the racial wealth gap. With the gap increasing in size as time goes on, policymakers must take immediate action through policy responses centered around making homeownership more accessible to Black populations. One policy option is to increase opportunities for down payment assistance to assist first-generation Black homebuyers in purchasing homes. Another option is to convert the home mortgage interest deduction to a one-time tax credit, increasing eligible mortgage payment benefits for Black households. The final policy solution presented is to expand the implementation of Small Area Fair Market Rents, which would increase mobility to opportunity-rich areas for Black families that hold housing vouchers. This brief recommends expanding the Small Area Fair Market Rent approach and reinvesting the funds saved in the federal budget to increase opportunities for down payment assistance. This recommended policy action will require collaboration between agents across federal, state, and local levels to boost Black homeownership rates and potentially close the racial homeownership gap.

INTRODUCTION

Many factors operate systematically to maintain and increase the racial wealth gap, but none widen the disparities in wealth between white and Black American families as much as housing inequity. The price of such inequity is not only tied to actual property— the disadvantage that comes with non-homeownership extends to all areas of life. Non-homeownership is linked directly to reductions in disposable income, barriers to business development, and a lack of opportunities to accumulate wealth intergenerationally. These factors compound exponentially to create a sizeable race-based difference in wealth and quality of life with time.

Past policy changes have been too infrequent and weak to tackle such a significant, deep-set issue. Policy solutions must erase the obstacles Black people face and address the root causes of the racial homeownership gap to increase Black homeownership on a meaningful, national level.

This brief analyzes some of the existing obstacles contributing to the racial homeownership gap to inform equitable policy responses and delivers a final recommendation to target these disadvantages and significantly increase Black homeownership rates nationwide.
The Racial Homeownership Gap

Homeownership is a fundamental driver of wealth accumulation and is often the only path for social mobility. From 2016 to 2019, housing wealth was the single biggest contributor to the overall increase in net worth, accounting for 32% of the increase across all income groups in the U.S. (Kushi, 2020). Its crucial role during these years demonstrates why racial inequities in homeownership have such far-reaching effects on the wealth and opportunities available to Black people. The Federal Housing Administration, or FHA, established in 1934 as a part of Roosevelt's New Deal, institutionally imposed segregationist practices onto the housing landscape by insulating new suburban communities against people of color. It refused to insure mortgages in and around predominantly African American neighborhoods through redlining, accelerating the decay of Black communities by weaponizing and withholding mortgage capital (Berkovec, 2018). These policies diffused through the private sector, such as banks and mortgage lenders, as private entities needed to follow FHA standards to qualify for insurance. The FHA created these policies to dramatically reduce Black homeownership rates to limit Black populations' economic opportunities.

While housing practices no longer employ methods as blunt as directly labeling predominantly minority areas as "unfit" in dark, red ink, the long-lasting implications of such practices continue to spiral unchecked to create even larger disparities. The Fair Housing Act of 1968 seemed to ensure there would be no identity-based discrimination in the sale or rental of housing, including on the basis of race and color. Yet from 1960 to 2017, the racial homeownership gap has only increased from a 27-percentage point gap (a white homeownership rate of 65% compared to a Black homeownership rate of 38%) to a 30-percentage point gap (a white homeownership rate of 72% compared to a Black homeownership rate of 42%) (McCargo, 2019). Moreover, from 2000 to 2017, Urban Institute data showed that the Black-white homeownership gap increased significantly in 105 metropolitan statistical areas (MSAs) surveyed, depicted in Figure 1 below.

In their 30s, white people have an average of three times as much wealth as Black people do at that age, averaging about $147,000 more. However, in their 60s, white people have an average of seven times as much as Black people do at that age, over $1.1 million more in average wealth (Urban Institute, 2017). The considerable increase in the gap primarily lies in the inability of most Black families to enjoy the passive wealth accumulation that comes with the appreciation of housing and land assets.

As wealth continues to unequally accumulate intergenerationally, the problem will become increasingly difficult to solve without direct, swift, and intentional legislation. In 2016, the net worth of the average white family ($171,000) was nearly ten times greater than that of the average Black family ($17,150) (McIntosh, 2020). The racial wealth gap only continues to widen, locked in a positive correlation with the ever-growing racial homeownership gap (Price, 2020). The obstacles surrounding homeownership create inescapable constraints within all spheres of life, such as education and disposable income, that impede Black Americans' efforts to build wealth at every turn. These systematic disadvantages significantly lower quality of life and place immense financial pressure on Black people, translating to a loss of consumption and spending in other areas of the economy.

As one of the most prominent forces in determining the distribution of wealth, taking policy action to help equalize homeownership will fix a
direct cause, rather than a mere symptom, of the racial wealth gap. Many non-homeowning Black Americans identify as renters and fall into lower-income groups. Therefore, increasing the accessibility of homeownership to lower-income populations and creating opportunities for renters to buy and own homes will directly increase the Black homeownership rate. Reducing the racial homeownership gap and equalizing opportunities will break the cycle of worsening racial wealth disparities.

Policy Options

**Increase opportunities for down payment assistance.**

One solution to this problem is to increase the amount of down payment assistance, or DPA, available and increase its accessibility to first-generation homebuyers. To accomplish this, Congress will first need to pass a bill appropriating funds from the Department of the Treasury to administer grants for DPA to first-generation homebuyers with incomes up to 120% of the median income. The majority of current Black non-homeowners have never previously bought a home, so using this criterion to identify DPA recipients along with the income parameters will ensure delivery of aid packages to Black Americans who require DPA most to purchase a home. State Housing Finance Agencies (HFAs) will distribute these grants and partner with Community Development Financial Institutions (CDFIs) to deliver precisely to underserved communities (Stegman & Loftin, 2021). The more specialized state-by-state delivery system of HFA grant distribution has proved useful in reaching communities of color with DPA without federal subsidies. In 2019, 29% of all HFA single-family purchase loans went to people of color (NCSHA, 2020).

This solution directly combats one of the biggest obstacles to Black homebuying. In 2019, Freddie Mac data estimated that more than 1.7 million mortgage-ready Black renters could afford to purchase a median-priced house in the 31 largest metropolitan statistical areas if they could put forward a 10% down payment (McCargo, Choi, & Golding, 2019).

Consumers receiving aid under this new program would also be required to complete a CDFI-approved homebuyer education program. This condition to receiving DPA ensures that this program will cause Black homeownership rates and wealth to increase intergenerationally by teaching financial literacy and wealth-building strategies, rather than merely a one-time artificial push in Black homebuying (OAHP, n.d.).

However, this policy solution may have unintended effects. DPA is at risk of being capitalized into higher housing prices, which would diminish its results. The effects of the pandemic on the housing market, such as severe market shortages, further exacerbate this risk (Parrott & Zandi, 2021). Most people receiving DPA would also still need additional forms of aid throughout the homebuying process, which usually take the form of loans. Loans with DPA have higher delinquency and insurance claim rates than similar loans without DPA, possibly because the homebuyer has less equity in the transaction (Goodman, Parrott, & Bai, 2016).

**Convert the home mortgage interest deduction to a tax credit.**

Another policy solution is to convert the home mortgage interest deduction, or HMID, to a tax credit. HMID is a tax break that allows itemizing homeowners to deduct mortgage interest paid on up to $1,000,000 worth of their principal mortgage amount. However, the tax break fails to reach a majority of homeowners, especially those of lower- and middle-level incomes, as most homeowners do not itemize and therefore reap no HMID benefits. 73% of claimed HMID benefits go to those homeowners with incomes over $100,000, as depicted in Figure 3 below.

The uneven distribution of benefits is not only class-based but extends to race as well: white households are much more likely to benefit from the HMID as they are more likely to be homeowners and have larger mortgages. In 2017, white households received nearly 78% of HMID’s benefits, while Black households only received six percent (Sullivan et al., 2017).

To implement this solution, federal legislators need to pass a bill to convert HMID to a one-time tax credit for mortgage interest for first-time homeowners.
homebuyers (Fischer & Huang, 2013). In addition, the legislators need to introduce an amendment that would lower the cap on the amount of a mortgage eligible for a tax break from $1 million to $500,000 (Baneman et al., 2011).

Converting HMID to become a one-time tax credit specifically for first-time homebuyers incentivizes Black non-homeowners to purchase a home as they would now receive previously unavailable benefits from their purchase. Lowering the cap on the amount of principal mortgage eligible to receive HMID benefits would also help concentrate welfare in lower-income demographics such as non-homeowning Black populations.

This policy solution is also cost-effective—the HMID in its current state is extremely expensive. The U.S. Treasury estimated it will reduce total federal revenue by $597.6 billion from 2019-2028. Converting it to a one-time tax credit and lowering the cap on the amount deductible will significantly reduce costs to the federal budget without decreasing potential HMID benefits for lower-income demographics (Viard, 2013).

Like the previous solution, this course of action must be contextualized in the current housing climate. Such a large reform is bound to create further instability in the housing market, which may be enough to significantly undermine its recovery when compounded with the effects of the volatile COVID-19 pandemic (Anenberg and Ringo, 2021). Additionally, HMID has been an unmoving piece of policy since its inception, so such an extensive reform has considerable political obstacles and is unlikely to pass with any tangible or real effect (Glaeser and Shapiro, 2003).

Expand implementation of Small Area Fair Market Rents (SAFMRs).

The final policy solution discussed in this review will be to expand the implementation of Small Area Fair Market Rents (SAFMRs). Currently, The Department of Housing and Urban Development, or HUD, benchmarks the value of housing vouchers to costs in the entire metro area, leaving prices much too high. Therefore, HUD must restructure its current Fair Market Rent (FMR) evaluation system to use the SAFMR approach, setting housing voucher payment standards at an individualized ZIP code level (Mathew, Rodrigue, & Reeves, 2016).

The current FMR system leaves many voucher holders unable to afford housing in lower-poverty and more opportunity-rich areas. A study of the SAFMR approach already executed by the Dallas Housing Authority found it has allowed more

However, SAFMRs can distort rent-setting in some areas when calculating rent values because HUD lumps together all units in each ZIP code. This methodology can (and does) result in artificially high SAFMRs in ZIP codes where smaller units make up most rental units and artificially low SAFMRs in ZIP codes where larger units are the majority (Fischer, 2015). To remedy this, HUD will need to partner with localized agencies (such as local-level governments, non-profits, HFAs, and CDFIs) to ensure the new benchmarks are accurate to need in ZIP codes and are being executed correctly by public housing authorities (PHAs) (Patterson & Silverman, 2019).

Another technical complexity of this solution is that large-scale expansion of SAFMRs requires a
drastic overhaul of how the HUD structures FMRs nationwide, which may offset any benefit of not requiring any congressional action.

**Recommendations**

The most feasible and helpful policy action to increase Black homeownership rates combines the first and last options. While converting the HMID to a one-time tax credit would help millions of Black Americans, it is simply not politically feasible as such a significant reform is very unlikely to pass in Congress.

First, HUD will need to gradually expand the use of SAFMRs by first targeting the metro areas with the largest difference between benchmarks against the entire metro area versus individualized ZIP codes, as these areas would benefit most. Local agencies, such as HFAs and CDFIs, will be partnered with HUD to prevent the artificial distortion of abnormally high and low rent-setting. This implementation of the SAFMR approach will result in money within the federal budget saved, which can then be reinvested into down payment assistance opportunities delivered through the same HFAs and CDFIs. These local institutions will be able to tie in the specialized delivery systems of both policy solutions to ensure that Black non-homeowners remain the central focus of the policy actions being taken. They will also increase transparency and communication down the line to PHAs executing the SAFMR benchmarks, ensuring the money saved from the shift to SAFMRs will directly be reinvested into equitable DPA targeted towards lower-income Black non-homeowners.

This policy action will allow both short- and long-term relief by first alleviating pressure on Black renters by allowing them to move to more opportunity-rich areas through the SAFMR evaluation system, and then supplying these families with the capital necessary to purchase and own homes through down-payment assistance. The SAFMR approach tackles the de facto segregation perpetuated by American society by allowing Black Americans to integrate into higher-opportunity, wealthier communities. To ensure that Black Americans can maintain their new foothold in these communities intergenerationally, a CDFI-approved homebuyer education program will be a requirement to receive DPA. This program will also minimize the risk of delinquency and insurance claims on loans taken by people who have received DPA by teaching financial literacy through the new lens of homeownership.

Other probable risks of the policy solutions, such as disruptions of the housing market and the possibility of DPA capitalization into higher housing prices, can be mitigated through the gradual implementation of the SAFMR structure and slowed dissemination of DPA grants to the public. The ability of HUD to freely make changes to the way they structure the FMR evaluation system means they can plan the pace of their shift based on direct reporting from the HFAs and CDFIs on how the current changes affect citizens in the housing market.

Black homeownership rates must be increased and maintained intergenerationally to create equitable opportunities. The racial homeownership gap has broad implications that permeate all spheres of life, reducing the quality of life of millions of Black Americans and costing them the chance to benefit from the critical driver of wealth accumulation. An intentional and swift policy change incorporating both federal agents and more localized entities is the only way to cut through the systemic racism that has disadvantaged Black people in the U.S. and make a tangible reduction in the racial homeownership gap.
References


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Rohan Tapiawala is a first-year student at the University of North Carolina at Chapel Hill, majoring in Pre-Business Administration and Public Policy. He hopes to use these two fields of study to reach the intersection of cross-sectoral collaboration, specifically the use of policy initiatives to support private and non-profit endeavors to close inequities in different policy arenas in both national and local contexts. This research project constitutes an analysis of possible policy solutions for closing the national racial homeownership gap through policy-side, private, and non-profit solutions.
The Quantification of Aneurysm Biomarkers Enables Enhanced Biochemical Monitoring for Aortic Aneurysm Disease

by John Cannon

Thoracic aortic aneurysms are a ballooning of the thoracic portion of the aorta, the large artery that carries blood away from the heart. Aneurysms can lead to aortic ruptures, which have a fatality rate above 90% even with immediate medical intervention. Currently, the only way to test for a thoracic aortic aneurysm is to perform a CT scan, which is expensive and exposes patients to ionizing radiation. An alternative test that is cheap, easy, and harmless would be an asset in the prevention of aortic aneurysm deaths. Testing the blood for biomarkers related to the formation of aortic aneurysms is one method of achieving such a test. When the tissue of the aorta balloons, it undergoes a physiological change; this change involves several microRNA and protein types, which can theoretically be detected in the blood. By detecting these microRNA and protein biomarkers, a diagnostic test for thoracic aortic aneurysms could be developed. Moreover, there are many different medical conditions that can lead to the development of aneurysms, such as Marfan syndrome or Turner syndrome. The biomarker profiles likely vary based on those conditions, as well as the sex of the patients. For these reasons, it’s crucial to calibrate the tests along these demographic lines; the test would not be “one size fits all”, but rather a more individualized element of medical care.

**Keywords:** Aorta; aneurysm; biomarker; microRNA; protein

**INTRODUCTION**

The aorta is the body’s largest artery, tasked with carrying blood away from the heart and throughout the circulatory system. It is divided into two distinct regions, which vary in structure, function, and response to physiological changes. These regions are known as the thoracic and abdominal aorta. When someone’s thoracic aorta is undergoing an aneurysm, defined as the diameter increasing by at least 50%, the artery may eventually rupture; this rupturing is often fatal. (Jonker et al. 2011) These thoracic aortic aneurysms (TAAs), however, are mostly asymptomatic until they have progressed quite a bit. For example, though the median age of diagnosis for TAAs is 65 years old, it is believed that its degenerative process and changes to the extracellular matrix begin much earlier. In patients with a genetic predisposition to TAAs, the median age of diagnosis is 56.8 years, though this is believed to be due to a closer monitoring of their aortas, rather than earlier development of the aneurysm.
The thoracic aorta is divided into the ascending segment, which brings blood upwards, and the descending segment, which brings blood downward. TAAs are known to grow at an average rate of 0.1 cm per year in the ascending TA and 0.3 cm in the descending TA; as the aorta increases in size, the likelihood of rupture significantly increases (Elefteriades, 2008). Once diagnosed, TAAs are allowed to grow until the risk of surgery is outweighed by the risk of rupture; typically, this is before the diameter reaches 6 cm in the ascending aorta or 7 cm in the descending aorta. If a TAA were to rupture, it is thought that up to 90% of patients would not survive. (Johansson et al., 1995) This is why early diagnosis is critical for the survival of patients. The only currently approved method for TAA testing is performing a CT scan. CT scans are a time consuming, expensive, and expose patients to ionizing radiation, which does not make them a convenient way to test for TAAs; many patients who are completely asymptomatic would never get a CT scan, and their TAA can progress without their knowledge (Computed tomography (CT) scans and cancer fact sheet 2021). Many patients who are diagnosed with a TAA only receive said diagnosis due to it being picked up during another test, for example, a CT scan performed for detection of other cardiovascular related diseases. An alternative approach for testing for TAAs is analyzing biomarkers in a patient's blood. When someone is experiencing a TAA, their aortic cells are undergoing a transformation; ballooning in the aorta is due to a change in the extracellular matrix of the aorta (Lindsey et al., 2003). This extracellular matrix is found in the middle of the three layers of the aorta, the tunica media, which is where to provide the elastic compliance that the aorta requires to function properly. When a patient is experiencing a TAA, their levels of elastin and collagen, two molecules constituting the extracellular matrix in their aorta, decrease. Elastin and collagen are typically long lasting components of the matrix with half lives measuring in decades, so their breakdown is atypical (Jones et al., 2009). Previous research analyzing proteins involved in this breakdown, both in tissue and in plasma, has uncovered some interesting findings regarding the different levels of specific proteins. These proteins are found in the matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) families, correlating with TAAs. (Ikonomidis et al., 2013) A diagnostic test that focuses on assessing the levels of these proteins in the blood would be cheaper and would not expose patients to ionizing radiation. There are several different risk factors associated with TAAs, some genetic and others behavioral. A history of nicotine use or genetic conditions such as Marfan syndrome have been shown to increase a patient’s likelihood of experiencing a TAA (Wagenhauser et al., 2001) (JS;, 2013). The most common congenital cardiovascular malformation, the bicuspid aortic valve present in 2% of the population, is known to disrupt normal aortic form and function, with nearly all having increased aortic dimensions and around 20% having full TAAs (Hahn et al., 1992) The proteins are involved in modulating the contents of the extracellular matrix; as an extracellular matrix is known to change when TAAs form, it follows that one may be able to measure these protein levels in the blood to diagnose a TAA. Specifically, MMP-1 and MMP-2 abundance in the plasma are known to be elevated in individuals experiencing a TAA, so the prior diagnostic research focused on measuring those proteins. (Barbour et al., 2007) It is known that certain small, noncoding RNA strands, known as microRNAs, are also present in the plasma and tissue when the thoracic aorta is experiencing an aneurysm, so assessing the levels of these microRNA molecules in conjunction with the protein is a specific focus of this research. MicroRNA functions as a post-transcriptional regulator of gene expression; they are indicative of a cell changing protein levels. The proteins will be analyzed using multiplex suspension arrays (MSA), which is the same technique utilized in previous research performed by this lab. (Ikonomidis et al., 2013) MSA works via biomolecular binding interactions between a sample which contains the target analyte, for example, human plasma containing MMP-1, and microbeads with ligand-specificities encoded in a suspension array. The microRNA will be analyzed using a digital droplet polymerase chain reaction (ddPCR), which is a version of typical PCR capable of providing absolute quantification with great accuracy and precision. ddPCR can provide the number of nucleic acid copies per unit volume. It achieves this by partitioning a single reaction into >20,000 individual droplets before the PCR itself takes place. It is possible that the diagnostic blood tests will not only be able to tell patients if they are experiencing a TAA, but also distinguish between subtypes of aneurysm etiology. Because it is so advantageous to identify patients experiencing a TAA early, it would be beneficial to be able to screen asymptomatic patients en masse. It is clear that CT scans are not a viable method for this, but a cheap, quick blood test would be. To develop this blood test, it would need to be possible to draw
a correlation from the levels of specific microRNA and protein molecules in the blood and the likelihood of a TAA to be present in the patient. It would also be beneficial if these biomarkers could be used to assess the cause of this TAA. Using these quantifications, a clinical test could ideally be developed to run using only a small amount of a patient’s blood. The quantification of aneurysm biomarkers enables enhanced biochemical monitoring for aortic aneurysm disease.

**METHODS**

**RNA Extraction**: To establish a method for normalization, an exogenous control sequence (Mir39) was added to the sample. From a plasma sample, Total RNA was extracted via ethanol precipitation and TRIzol Reagent (15596026, Thermo Fisher Scientific, Waltham, MA), followed by an initial quantification using NanoDrop 2000 (Thermo Fisher Scientific).

**ddPCR**: From extracted microRNA, cDNA was generated using a Master Mix composed of Dntp Mix, RNase Inhibitor, 10X RT Buffer, Multiscribe Reverse Transcriptase, Mir39 Primer RT (20X), MiR133a Primer RT (20X). This was mixed with samples in a PCR tube and placed in a thermocycler. For primary microRNAs, cDNA was not diluted prior to droplet generation and polymerase chain reaction amplification. The purpose of these dilutions was to allow for a minimum count of 100 copies of each individual RNA copy to be measured for each ddPCR reaction. 5 μL cDNA sample, 1.25 μL ddPCR supermix for probes (no dUTP) (1863024; Bio-Rad Laboratories, Hercules, CA), and 5 μL RNase-free water was added to each ddPCR mixture. In addition, .25 μL miR133a Fam labeled probe and 1.25 μL U6 VIC labeled probe were added for microRNAs.

**Multiplex Suspension Array**: The MSA kits utilized were: FCSTM07, and LKTM003 from R&D Systems. Plates were then read using a Bio-Rad Bioplex-200 analyzer, and the results were compared to a standard curve on the same plate.

**Data Analysis**: SYSTAT (SigmaPlot – Statistical Analysis version 14) was used to perform statistical analyses. Student’s t-test and Welch’s t-test were used as two different sample mean comparisons. If different p-values were obtained, the higher of the two values was reported.

**Sample Population**: Plasma samples were obtained from a Human Plasma Repository, a collection of de-identified human aortic tissue and plasma samples stored in-house and provided by NHLBI Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC). All released data and specimens had been collected by the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC). 761 patients with aneurysms with different etiological subtypes and 364 patients with no diagnosed AA made up the sample. The etiological subtypes sampled were: Marfan syndrome, Turner syndrome, Ehlers-Danlos (vascular) syndrome, Loeys-Dietz syndrome, familial thoracic aortic aneurysm, and bicuspid aortic valve without family history.

**RESULTS**

Figure 1. TIMP MSA Results: The top row contains a list of MMP family proteins that were chosen as analytes, and the left column lists the underlying conditions associated with the aneurysm. Analyte concentrations ± standard error of the mean (SEM) are listed in each cell, with the sample size and the average age ± SEM for the age. Data for both the total and each sex are separated by rows. Statistically significant differences between the results and a control group are marked by an asterisk (*) and the hashtag (#) represents differences in data for the sexes (p < 0.05).
**CONCLUSION**

**Protein Data**

The protein data contain a number of meaningful findings. Protein data are available for each underlying condition that is being studied. Moreover, data were able to be obtained for nine proteins in the MMP family and four proteins in the TIMP family. Of these, different proteins provided statistically significant results for different protein populations, with certain proteins, such as MMP-2, MMP-9, and TIMP-2 having statistically significant levels for a majority of TAA etiologies. Others, such as MMP-12 and TIMP-4, provided no statistically significant data at all. First, for the TIMP family, TIMP-1 had statistically significant changes for all profiles except for Turners and Ehlers-Danlos, and TIMP-2 produced statistically significant results for all underlying conditions. BAV and FTAA data also contained a significant difference between male and female results for TIMP-1. For the MMP family, MMP-2 produced statistically significant results for all populations except female patients with Ehlers-Danlos, a blindspot only covered by TIMP-2. MMP-2 also displayed statistically significant differences between sexes in BAV patients. Other proteins provided statistically significant results for a smaller selection of patients, such as MMP-13 only providing significant results for BAV and male FTAA patients, but these can be of use for patient populations in those demographics.

Although this data does not directly function as a diagnostic test, it indicates the proteins of interest that could be used to potentially create such a test. Moreover, it illustrates that protein levels are not standard across TAA patients and do break down along subtypes as was predicted. This is promising, as it supports the idea that a diagnostic test will be able to determine underlying etiology as well as the presence of the TAA itself. There were also several notable instances of significant difference in results for male and female patients. This underscores the importance of a representative sample of people, as sex based biology differences evidently influence certain protein levels in these TAA patients.

The statistical significance of the change in protein levels indicates that it is likely these proteins are playing some role in the development of the aneurysm itself, as the proteins are of a family known to be involved in ECM regulation. This data supports the idea that, as a result of decreasing collagen and elastin levels, certain proteins involved in this process will be elevated in the blood. It's worth noting that measuring the elevation of individual protein levels is only a step in the process; the goal is to create a biomarker profile featuring protein and RNA that we can use to assess the samples.

**microRNA Data**

Further data about the RNA levels is necessary to draw firm conclusions. The exact RNA extraction and quantification protocol are still being developed, and as such, there is no usable data. In order to account for variability in extraction, as well as in the assay technique itself, a control microRNA is going to be added to the sample to allow for normalization across these variables. For this purpose, Mir39, a microRNA, is going to be used as the exogenous control. Exact usage of the Mir39 exogenous control has not been fully developed, and the proper purification protocols are still in the works, as currently the data is experiencing fluorescent interference.

**FUTURE DIRECTIONS**

Although this data is promising, there is still a long way to go before a full diagnostic blood test is developed. MicroRNA data to supplement the existing protein data is an important next step. After that, clinical trials are crucial for determining if such a test actually functions when utilized in a healthcare setting. Should these results both be successful, a possible direction would be to broaden the scope of the diagnostic test, perhaps to include other types of aneurysms. Alternatively, further research could be completed to improve the accuracy of the diagnostic test. All of this is reliant on continued research into these biomarker tests.
Bibliography


Taking a New Lens To Augmented Reality and Oral Health

by Parth Patel

The aim of this scoping review is to review how augmented reality (AR) is used in various clinical settings, specifically in dental care. The methodology of this scoping review is based on the framework that is outlined by Arksey and O'Malley [22] and recommendations from Levac et al [21]. The review included five key phases to review each form of literature related to AR. The results from our search populated 31 articles. Among the remaining articles, 19 studies were used to analyze the implementation of AR technology in different clinical settings of dentistry. These majority of articles examined oral and maxillofacial surgery along with general surgery. There was minimal literature present in pediatrics and other specialties. This work provides a detailed review of the future implications for AR in dentistry as it is a promising and growing technology. AR dentistry can positively impact patients in all clinical settings of dentistry because of its practical applications. Although there remain various barriers as to whether this shift will occur in all dental offices, this technology is still making a direct impact on dental patients worldwide.

Keywords: Augmented reality, Maxillofacial surgery, Implantology, Education, Orthodontic

INTRODUCTION

The medical field has experienced copious amounts of growth in technological advancements in the recent few decades. For example, artificial intelligence (AI) provides another set of eyes which allows for a validation of clinical decision making in a dental clinic [1]. It uses a plethora of algorithms to make informed decisions on how to proceed with a dental case. This increases the general population’s level of comfort with the advancements that have taken place in the past few decades.

A prominent piece of technology used in various procedures in the medical field is Augmented Reality (AR). AR combines virtual objects within the real world, offering possibilities for the simulation of real objects and spatial visual feedback to the user. This technology can aid in training and knowledge acquisition [2]. In contrast with virtual reality (VR), where the user is immersed in a digital environment, an AR user experiences reality in real time, where all human senses respond to real world stimuli enhanced by virtual elements [3].

From a historical perspective, one of the first approaches to AR was an AR head-mounted display system and provided cinematic experience through various senses [23]. Augmented reality is commonly used in various medical fields [2], and these systems have allowed for a more efficient simulation of a three-dimensional model which permits a stronger interaction with the patient [3] or during a training session.

Augmented Reality is slowly being implemented in various specialties in dentistry, such as
prosthodontics and oral maxillofacial surgery, where its implementation allows for stimulation of diverse functions and movements without invasive steps [1]. Moreover, dental surgical Augmented Reality is slowly being implemented in various specialties in dentistry, such as prosthodontics and oral maxillofacial surgery, where its implementation allows for stimulation of diverse functions and movements without invasive steps [1]. Moreover, dental surgical techniques are performed with more precision by using a predesigned surgical template from AR which ultimately circumvents human error [1].

Since AR is a new form of technology in dentistry, its overall effectiveness in a clinical setting is still not well-known. This scope review aims to describe how oral health care is being transformed by a digital approach using AR in various specialties in dentistry and in a wide range of common dental procedures.

METHOD

The methodology for this scoping review was based on the framework outlined by Arksey and O’Malley [22] and ensuing recommendations made by Levac et al [21]. The review included the following five key phases: (1) identifying the research question, (2) identifying relevant studies, (3) study selection, (4) charting the data, and (5) collating, summarizing, and reporting the results. The optional ‘consultation exercise’ of the framework was not conducted. A detailed review protocol can be obtained from the corresponding author upon request.

The results obtained from our search populated 31 articles. Among those results, there were 12 studies that were not applicable because they did not match the scope of this review (Figure 1). The scope omitted literature published before the year 2000, literature that focused on virtual reality, and articles that lacked a full study. Among the 15 accepted studies that the researchers agreed on accepting, a plethora of useful data relating to the implementation of AR technology in different areas of health was obtained (Table 1).

Research question

This review was guided by the question, ‘Is there evidence in the literature suggesting the use of AR leads to better oral health care?’. For the purposes of this study, a scoping review is defined as a type of research synthesis that aims to display literature on a particular topic and extrapolate the key concepts from it. This includes gaps in the research, evidence to inform practice, policy making and research. [20].

Data sources and search strategy

The initial search was implemented on the PubMed electronic database and the ACM digital library. The keywords used were: “augmented reality; oral health”; “dentistry”. The availability of information related to AR in dentistry is scarce and this resulted in a broader scope review, including AR used in other facets of medicine, i.e., general surgery [6], anesthesia [12], and oncology [13]. However, with the search we conducted, the results that populated were effective in aiding our research as far as what AR technology has been used for thus far in the health sector, as well as studies being performed similar to ours.

RESULTS

Oral maxillofacial surgery was the discipline in which AR seemed to be implemented the most [5], [16], [17]. Several studies focusing on the application of AR to behavioral and surgical procedures were also conducted [10], [2], [4], [13], [7]. Two studies [2], [4] were specifically related to the research question, “Is there evidence in the literature suggesting the use of AR leads to better oral health care?”. For example, one article discussed that using a toothbrush was connected to augmented reality in order to promote the oral health of those with cleft lip palate [5]. However, since this study was in its early stages, it did not provide enough results to find any meaningful conclusions. The other article that was associated with the focus of this review developed a toothbrush game using AR technology to improve oral hygiene among 6 to 10 year olds [2]. However, the evaluation of the effects of this technology on oral hygiene had not yet been performed. Table 1 contains the accepted journals and a brief review of each study.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Objective</th>
<th>Area in Dentistry</th>
<th>Type of AR technology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aryeh et al. (2017) [5]</td>
<td>Evaluate the efficacy of AR in increasing accuracy of dental implants and navigational skills</td>
<td>Maxillofacial surgery</td>
<td>AR (developed by Intra Oral and Leap motion devices)</td>
<td>Augmented reality increased the accuracy of dental implants, as well as intraoperative navigational skills, and overall improved the planning of procedures</td>
</tr>
<tr>
<td>Amarouche et al. (2020) [2]</td>
<td>Improve oral hygiene in children age 6 to 10 via interactive toothbrush game</td>
<td>Pediatric</td>
<td>Game (developed by Microsoft Corp.)</td>
<td>Study not completed yet</td>
</tr>
</tbody>
</table>
Table 1. This table summarizes the literature that uses AR in a dental setting. The results from using AR in each dental specialty is summarized.

**DISCUSSION**

AR and VR have very similar qualities, yet the benefits of AR are superior to VR in the realm of retaining science-based knowledge via visual and auditory stimulation. In a study performed by Huang, et al., college students were tested on their retention of specific knowledge; in the two conditions, one group of students used VR, and the other used AR [8]. Although VR was found to be useful in information retention, AR provided more benefit than VR when auditory information was added. Overall, the results from the study revealed that AR was more effective in retaining information. Researchers suggested that this result was partly due to the increased cognitive demands associated with the immersive properties of VR, as well as the spatial presence playing a part in its success. To conclude, prior research suggests that when students are only being exposed to visual information, VR can be useful, but if auditory information is also a part of the environment, then AR is more effective in consuming the information being relayed by educators.

The application of AR in dentistry can be seen as the more effective modality for relaying information from the computer directly to the vision of the dentist. Not only is it successful in helping retain information via cognitive demands, but also it is also useful to improve dexterity. A study in which AR technology was designed to test the efficacy of AR in surgery revealed that AR was successful in decreasing loose knots and broken sutures [9]. This significantly decreases external factors affecting a dental surgery and augments surgery success rate.

Of the results collected, what could be gathered was data on the different AR technology currently being used, or was used, as well as the different disciplines in dentistry that have used this technology. Among various dental specialities, AR decreased visualization error, time of procedure, and improved overall accuracy. Augmented reality is becoming prominent not only in dentistry but various other healthcare fields as a tool for training.
residents in general surgery [6], anesthesia [12], and oncology [13].

The game-based AR tech that was found was Kinect [2], created by Microsoft corporation, and Kolibree Pro [4] software which used gamification in combination with AR to study the effects of these variables with improving the oral health of children [4]. Despite various studies still in progress, preliminary results reveal positive outcomes during dental surgery with the use of AR. Other emerging technologies that are similar to AR technology were identified as VR surgery [5], Block Matching Algorithm (BMA) [6], Iterative Closest Point (ICP), and Mixed Reality (MR) [7]. These technologies were implemented in OMS, dental implantology, anesthesia, X ray system and alveolar bone analysis, and general surgery and provided success during various dental procedures. Although in its very early stages of implementation in the health sector, AR has been proven to provide an additional assistance to create more effective surgical techniques. From providing confidence in third year surgical residents, to improving the error rate among jaw surgeries, this technology has a place in the health industry.

**CONCLUSION**

This work provides a detailed review of the future implications for the use of AR in dentistry. AR dentistry can positively impact a wide array of people including dental practitioners and their patients. Various assessments and uses in clinical settings epitomize that AR is becoming more common in practical applications.

Augmented reality is a growing and promising technology that will positively impact a plethora of patients. With new technology created for augmented reality, the technology will work more efficiently and create more opportunities for dental practitioners to perfect their work. A question remains as to whether the transition to augmented reality will occur or whether dental practitioners will stick to traditional methods. Nevertheless, augmented reality is a promising technology that shows favorable results and could soon be implemented in a clinical setting more prominently.
About the Author: Parth Patel

Parth is a third-year undergraduate student majoring in Neuroscience who works as a research assistant studying Augmented Reality (AR) in the UNC Adams School of Dentistry in the department of Diagnostic Sciences. With AR as a new form of technology, this scope review was created to summarize current literature in dentistry under the guidance of Dr. Ribeiro.
Impact of Nitriloacetic Acid (NTA) and EDTA on Zinc Stress Tolerance and Plant Growth in Pisum sativum (var Bohun) by Kevin Agner & Michael Larkins

Contamination of soil by heavy metals represents a major concern for environmental and human safety. Zinc, as a by-product of many human processes, is a significant source of this pollution. The chelating agent nitriloacetic acid (NTA) was investigated for its use in chelation-assisted phytoremediation to reduce Zn contamination. Pisum sativum var Bohun seedlings were grown hydroponically and exposed to either NTA or ethylenediaminetetraacetic acid (EDTA); the impact of these substances was investigated on plant growth and Zn uptake and compared to controls. Plant growth, relative water content, biomass change, and hydrogen peroxide content measurements were mostly inconclusive between all four variants, though EDTA- and NTA-treated plants had slightly increased germination rates (6 and 3% higher, respectively). EDTA- and NTA-treated plants had increased superoxide concentrations in leaf, though results were mixed with root. The chlorophyll content among all four variants was largely consistent, though the EDTA- and NTA-treated plants along with the control plants all had decreased chlorophyll b contents. The mixed results from this study are inconclusive as to the impact of NTA versus EDTA on Pisum sativum var Bohun growth, though both substances do contribute to increased plant stress.

Keywords: Heavy metal toxicity, zinc, chelation, phytoremediation

INTRODUCTION

Soil and water contamination from heavy metals has increasingly become a concern for the environment, human safety, and food security in recent times (He et al. 2015; Hu et al. 2017). Contamination by heavy metals affects the production and quality of crops, and through inclusion in food chains, it affects animal and human health. This type of pollution is long-lasting and irreversible. Furthermore, heavy metal contamination has been estimated at costing approximately $10 billion USD per year globally due to losses in industry and human/environmental health (He et al. 2015). Currently, about five million sites covering ~500 million ha of soil are contaminated with heavy metals (Lu et al. 2018). This includes a variety of heavy metals, such as As, Cd, Pb, Co, Cr, Hg, Cu, Ni, Zn, and Se (He et al. 2015). Common sources of such heavy metal contamination include mining activities, warfare, and chemical fertilizer use; urban areas are subject to
Zinc is an element commonly found in the Earth’s crust and is counted as one of the essential micronutrients for plants (Gondal et al. 2021). Its excess, however, can cause adverse effects on plants, such as impaired germination and growth, inhibition of photosynthesis, chlorosis, and micro- and macronutrient imbalances (Ghorai et al. 2019; Sidhu 2016). After Al and Mn, Zinc is cited as a major source of heavy metal contamination in soil. Kabata-Pendias and Mukherjee (2007) compiled the highest reported concentrations of some heavy metals in contaminated soils of industrial origin; for North America, it was shown that the United States has sites with the highest concentrations of Cd, Pb, and Zn compounds (at 1,500, 13,000, and 80,000 mg/kg, respectively), while Canada has the highest concentrations of Cu and Ni at 3,700 and 26,000 mg/kg, respectively. It is important to note that the United States Environmental Protection Agency (EPA) classifies Zn as a priority pollutant among 126 other offending substances (Protection of Environment, 2014). The primary anthropogenic sources of zinc in the environment include agricultural use, smelting, incineration, mining, and the widespread use of galvanized products. This contamination exerts a phytotoxic effect mainly via interference in chlorophyll biosynthesis, and through Fe-deficiency and interference in auxin and protein biosynthesis, excess of Zn negatively impacts P, Ca, Cu, and Mn homeostasis, synthesis of ATP, and carbon fixation (Nagajyoti et al. 2010; Mossa et al. 2020).

Given the impact of heavy metal contamination, removing heavy metals from soil has great potential benefits worldwide. Two general categories for addressing heavy metal contamination exist: physicochemical methods and bioremediation. Physicochemical methods generally utilize a physical/chemical process, such as incineration (Traina et al. 2007), adsorption/chelation (Naushad et al. 2018), or ion exchange (Naushad et al. 2015). These methods are effective, though they often result in secondary contamination of groundwater or air and can carry a high cost to utilize, limiting their effectiveness (Chaney et al. 1997; Sivarajasekar and Baskar 2015; Sivarajasekar et al. 2018). On the other hand, bioremediation consists of using natural organisms to reduce pollution (Vijayalakshmi et al. 2018). This can be further classified as in-situ (contaminants treated directly on-site) or ex-situ (contaminants treated after being transported from the site of contamination; Paz-Alberto and Sigua 2013; Ramachandran et al. 2013). Techniques included in bioremediation include bio-leaching (Rohwerder et al. 2003), bio-filtration (Journois et al. 1994), and phytoremediation (Muthusaravanan et al. 2018).

Phytoremediation utilizes plants (e.g., trees, shrubs, monocotyledonous and dicotyledonous plants, which can be tolerant, hyperaccumulators, or genetically modified) to restore contaminated land and/or water sources (Parmar and Singh 2015). The mechanisms by which this process works include: phytoaccumulation (contaminants are absorbed into the species along with nutrients and water and accumulated in tissues), phytostabilization (plants immobilize contaminants in soil, usually via their root structure and exudates), phytovolatilization (plant species absorb a contaminant, transform and release it into a less toxic form into the atmosphere), and phytodegradation (plants uptake and break down organic contaminants into less harmful metabolites; Muthusaravanan et al. 2018). Some key advantages of using phytoremediation include its low cost, reliance on free sunlight, long duration of effect, and the advantage of it reducing soil erosion concurrently. Phytoremediation is limited by the depth of root penetration by the species utilized, increased time for the process to take effect, and the production of potentially hazardous biomass unless appropriately handled.

It has been shown that the two aforementioned methods for addressing heavy metal contamination in soil, physicochemical methods and bioremediation, can be combined for synergistic effects, specifically in the case of chelating agent-assisted phytoremediation (Dipu et al. 2012). Chelating agents (molecules that bind to heavy metals) have been shown to improve heavy metal uptake in plants during phytoremediation experiments; examples include citric acid, EDTA, etc. (Asadzadeh et al. 2018). Over the years, EDTA has been specifically researched due to its high affinity for metal ions and its ability to increase the transport of EDTA-metal complexes from the soil to the upper portions of plants. EDTA has been shown to improve the uptake of Cd, Pb, and Zn specifically (Fard et al. 2013). However, because of EDTA toxicity as well as its longevity and mobility in the soil, and hence the risk of the rapid spread of contamination and infiltration into groundwater, EDTA is now used mostly as a reference for assessing the effectiveness of other chelators. Alternative chelating agents have been investigated for use in phytoremediation, including microbes and their products (Langella, et al. 2013). This paper focused on investigating the use of nitrilotriacetic acid (NTA), and comparing it as a chelating agent to EDTA in phytoremediation.
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superoxide anion content, and hydrogen peroxide anion determination were all carried out to better study the effect of NTA on Zn uptake and the effect of NTA on plant growth. Pisum sativum var Bohun was selected for this experiment as it has been found to tolerate increased Zn in soil (Kunjam et al. 2015).

MATERIALS AND METHODS

Materials

Pea seedlings (Pisum sativum var Bohun) were grown hydroponically in a perlite base for 7 days in a growth room with a 16/8 h photoperiod, day/night at room temperature, and light intensity of 82 mmol m\(^{-2}\) per s; plants were watered every day with 150 mL of 100 x diluted Hoagland medium per pot. Then, the plants were treated with stress factors in the following combinations:

- Variant 1 - control plants
- Variant 2 - 40 μM ZnSO\(_4\) solution
- Variant 3 - 40 μM ZnSO\(_4\) + 40 μM EDTA (Ethylenediaminetetraacetic acid)
- Variant 4 - 40 μM ZnSO\(_4\) + 40 μM NTA (Nitrilotriacetic acid)

Each variant had two groups of four seeds per experimental setup, for a total of 32 seeds. The experiments for each variant were carried out four times each.

Sample Collection/Weighing

The plants were collected after 48 h of cultivation with stressors. Heavy metals that accumulated on the surface of roots were removed by rinsing plant roots with 10 mM EDTA and deionized water. Treated plants were weighed, the length of roots and stems was measured, and chlorophyll and relative water content tests were carried out (see below); multiple samples were taken from each specimen to facilitate all required tests. The changes in biomass growth were determined by measuring the mass of all plants after the designated growth period. Results were presented as g fresh weight per plant.

Index of Tolerance

The index of tolerance (IT) was calculated according to Wilkins (1956):

\[
IT = \left[ \frac{\text{average length of roots in tested solution}}{\text{average length of roots in control solution}} \right] \times 100\%
\]

Superoxide Anion Determination

Superoxide anion content was determined using the method described by Doke (1983). The plant roots (0.3 g) were placed in the test tubes and filled with 3 mL of a mixture containing 50 mM buffer of K2HPO\(_4\) with 7.8 pH; 0.05 % NBT, and 10 mM of NaN3. The test tubes were incubated in the dark for 5 min, and then 2 mL of the solution was taken from each tube and heated up for 15 min at 85 °C. The samples were cooled with ice for 15 min and the absorbance was measured at the wavelength of 580 nm for the control (via a blank probe - buffer K2HPO4/KH2PO4 of pH 7.8).

Hydrogen Peroxide Determination

Hydrogen peroxide content was determined using the method described by Becana et al. (1986). Approximately 0.3 g of roots were homogenized with 5% trichloroacetic acid (TCA) at 4 °C. The homogenate was centrifuged 2 times at 13,500 x g for 10 min at 4 °C. The supernatant was filtered through a 0.45-μm Millipore filter.

The reaction mixture contained: 2 mL of 50 mM buffer 1 pH 8.4, 100 μl of the preparation, and 1 mL of the colorimetric reagent that was last administered. The composition of the colorimetric mixture prepared immediately before the measurement, was: 0.6 mM 4-(2-pyridazole) resorcinol and 0.6 mM titanic potassium oxalate. The reference samples contained 100 μl of 5% trichloroacetic acid. The decrease in absorbance was measured at 508 nm. The amount of hydrogen peroxide was presented in nmol H\(_2\)O\(_2\) per min per mg (fresh weight) in the extracts.

Chlorophyll a and b Determination

The levels of chlorophyll a and b were determined using dimethyl sulfoxide (DMSO) according to Ronen and Galun (1984). Leaf tissue (200 mg) was cut into small (4-16 mm\(^2\)) pieces and placed in a vial with 5 mL DMSO. Three replicates of each sample were incubated in a water bath at 65 °C for 120 min. Chlorophyll extract was transferred to a cuvette and measured via spectrophotometer; readings were made at 649 nm and 665 nm. The following formulas were used to determine chlorophyll a and b content:

\[
\text{Chlorophyll a: } (12.9*A_{665} - 3.45*A_{649})*50 \text{ [µg*g}^{-1}\text{]}
\]

\[
\text{Chlorophyll b: } (21.99*A_{649} - 5.32*A_{665})*50 \text{ [µg*g}^{-1}\text{]}
\]

Where A\(_{665}\) and A\(_{649}\) were the absorbances at 665 and 649 nm, respectively.

Relative Water Content (RWC)

The samples for RWC were weighed immediately as fresh weight (FW), then floated in distilled water for 4 h. The turgid leaf discs were rapidly blotted to remove surface water and weighed to obtain turgid weight (TW). The leaf discs were dried at 60 °C for 24 h, and then the dry weight (DW) was obtained. The RWC was calculated using the following formula:

\[
\text{RWC (%) } = \frac{(W-DW)}{(TW-DW)} \times 100
\]
Where, \( W \) = Sample fresh weight; \( TW \) = Sample turgid weight; \( DW \) = Sample dry weight

It was reported that this method should normally result in about 2% to 3% of RWC being a statistically significant difference between treatments.

RESULTS AND DISCUSSION

Zn is one of the basic elements involved in several important processes, including being a significant activating and regulating factor for many enzymes as their cofactor; zinc is involved in the control of the formation of chlorophyll, auxins, and growth-regulating compounds, and is essential for protein and starch production. Due to its diverse functions, both an excess and deficiency of Zn cause a number of often unfavorable changes in plant metabolism. The presented results show the effects of treating \( Pisum sativum \) plants with Zn ions with and without the synthetic chelators EDTA and NTA. The conducted experiments showed that all variants affected, to varying degrees, the basic physiological parameters and ROS levels of treated \( Pisum sativum \) plants compared to control plants (Tables 1-2).

Pea Plant Germination Potential

For each variant and replicate, the germination level of the plants in each pot was monitored. Each variant [Control, + Zn, Zn + EDTA, and Zn + NTA] was grown in two pots with four seeds each, for 32 individual pea plants per batch. The overall average germination potential was then calculated and presented in Table 1. A similar level of germination was obtained in all variants.

Table 1. Changes in physiological parameters in \( Pisum sativum \) plants grown under control conditions and treated with 40 \( \mu \text{M} \) ZnSO\(_4\) with or without EDTA and NTA for 48h. Mean values and SD were calculated from three independent experiments.

Relative Water Content (RWC) and Biomass Change

Relative leaf water content is commonly used to describe the hydration status of plants; this parameter is sensitive to several factors such as temperature, light, moisture, and water supply. This correlates closely with plant physiological activity and soil water status (Ozkur et al. 2009) and is a reliable determinant in screening different genotypes for drought tolerance. Relative water content can approximate the amount of water in a sample and thus can indicate the number of nutrients absorbed. The RWC results presented in Table 2 show very little change between the variants. The lowest level of RWC was determined for plants grown with Zn added; the values obtained for leaves of plants treated with Zn + NTA were similar. On the other hand, plants treated with Zn + EDTA had the highest values of RWC. However, considering that all results are within 0.5-2% of each other, within the error range for this measurement, no differential conclusions can be drawn on their basis.

One of the general responses plants have to stress is growth reduction, which is considered an essential component of assessing plant tolerance.
and a prime indicator of physiological response in plants (Malar et al. 2015).

The presented study exhibited an increase in the fresh weight of pea plants in all tested variants. The greatest increase was noted for plants cultivated with only Zn and Zn + NTA, with 42-47% growth compared to controls. The smallest increase in fresh mass (17%) was demonstrated in the variant Zn + EDTA. The observed effect of elevated biomass growth is probably moderated by stress and the relatively short time plants were exposed to stress factors. In most studies, unlike this article, plants treated with chelating agents experienced decreased growth when the wet plant weights were assessed (Ovečka and Takáč 2014; Kalaivanan and Ganeshamurthy 2016). However, a significant reduction in growth was observed when the level of dry matter in the tested variants was analyzed. All tested combinations showed a 72-78% decrease compared to the control plants. This effect may be connected to a decrease in photosynthetic efficiency and is common in plants exposed to heavy metals (Maksymiec and Krupa 2006; Rodríguez-Serrano et al. 2009; Sharma and Dietz 2009). In treated plants, it was also observed that the growth of leaves and roots was slightly altered. The root lengths for +Zn and Zn + EDTA variants were similar to the control plant; only Zn + NTA variants decreased by 18% compared to the control noted.

On the other hand, the stems in all tested variants saw a growth extension of 6, 11, and 28% for Zn, Zn + EDTA, and Zn + NTA, respectively. Generally, most authors examining various plant species exposed to heavy metals saw a sharp decrease in the growth of plant leaves and roots (Soudek et al. 2014; Muratova et al. 2015). The rather moderate or even positive effects of the presence of Zn observed in the presented experiments may be related to the relatively low concentration of Zn, short exposure time, and the status of Zn as an element necessary for the proper functioning of plants in general.

**Chlorophyll a and b Content Determination**

Chlorophyll a and b content were determined based on the procedure outlined in the Methods section of this paper. The chlorophyll content in plant species is directly linked to the ability to carry out and efficiency of photosynthesis. Reduced chlorophyll content can be indicative of increased stress and a disturbance of the mineral balance in plants. Zn can significantly decrease the activities of photosystem II (PSII) and, to a lesser extent, also of photosystem I (PSI) as well as the rate of photosynthetic electron transport (Kalaji et al. 2016). For chlorophyll a, in all tested variants a mild decrease in the amount of pigment was seen (12-16%) in comparison to the control. The chlorophyll b content in variants, on the other hand, was much lower compared with the control plants. The most significant decrease was demonstrated in the leaves of plants grown with Zn (66%) and Zn + EDTA (61%). A slightly higher level of chlorophyll b was measured for the Zn + NTA variant, where the decrease was 54% compared with the leaves of the control plants. This could be indicative of a stress response, or perhaps is the result of a metabolic effect from the presence of Zn.

**Superoxide Anion Generation in Pisum sativum leaves and roots**

The superoxide anion content was determined based on the procedure outlined in the Methods section of this paper. Many data indicate that heavy metals induce higher levels of reactive oxygen species (ROS) in plants, which is often the first indicator of stress status (Hu et al. 2012). In the present experiment, superoxide anion concentrations were measured in the roots and leaves of treated plants as presented in Figure 1.

**Figure 1.** Levels of A) O2^- (A580 g-1 fresh weight) and B) H2O2 (nmol·g-1 fresh weight) in roots of Pisum sativum grown hydroponically in control conditions and in the presence of 40 μmol Zn with or without EDTA or NTA for 48 hours. Mean values and SD were calculated from three independent experiments.
The presence of metals, directly and indirectly, leads to increased generation of ROS and consequently adverse changes; at high concentrations, ROS damage proteins, lipids, and nucleic acids. However, ROS also function as effectors and regulators of programmed cell death, as well as affecting the expression of many genes, explaining their role in the genetic stress response of plants (Malecka et al. 2014; Dalvi and Bhalerao 2013). High concentrations of superoxide anion can be indicative of a high-stress response in pea plants, and this testing allows for an observation of the effect a specific treatment has on plants. In the roots of plants in all variants, the amount of superoxide anion was similar to levels in the control samples. This may indicate that the zinc concentration applied is at a level with which natural antioxidant enzymes such as superoxide dismutase and low molecular weight antioxidants such as glutathione can cope. However, to confirm this, it would be necessary to monitor both the activity of the antioxidant system and the adverse effects of ROS, such as lipid proliferation and protein oxidation (Malecka et al. 2012). On the other hand, a significant increase in superoxide anion radical levels occurs in the aboveground parts of all the variants studied in comparison with the control plants. It is especially visible for plants treated with Zn + ligand complexes. In these plants the level of anion radical was for Zn + EDTA and Zn + NTA, respectively, 3 and 4 times higher than in control and + Zn plants. This effect may be related to the higher level of Zn accumulation in aboveground plant structures) the breakdown of metal-ligand complexes and the release of Zn ions. This is compatible with the observed significant reduction in photosynthetic pigment levels (Table 2).

**Hydrogen Peroxide Content Determination**

The hydrogen peroxide content for pea plant samples was determined based on the procedure outlined in the Methods section of this paper and can be seen in Figure 2.

It is important to note that both an average calculation and a line-of-best-fit calculation with the hydrogen peroxide concentration were done to compare the concentration data.

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**Figure 2** Levels of A) O$_2^-$ (AS80 g⁻¹ fresh weight) and B) H$_2$O$_2$ (nmol·g⁻¹ fresh weight) in leaves of Pisum sativum grown hydroponically in control conditions and in the presence of 40 μmol Zn with or without EDTA or NTA for 48 hours. Mean values and SD were calculated from three independent experiments.

The average calculation was done using an average from each measurement based on an auto-generated Excel (2016, Microsoft, Inc.) formula using the H$_2$O$_2$ concentrations from a calibration curve, with an R² value of 0.9404:

H$_2$O$_2$ Concentration (µM) = 0.1049*ln(A508) + 0.2595,

Where, A508 is the average absorbance at 508 nm.

The line-of-best-fit calculation was done using an average of the experimental values, which were then used for calculating the hydrogen peroxide concentration using the same Excel formula. The high R² value is indicative of a good fit for the data. It can be seen that while not exact, the formula values are close to those of the average values.

The hydrogen peroxide concentration can indicate plant stress in a similar way to the superoxide anion content previously discussed. The hydrogen peroxide concentrations appear similarly for most samples’ leaves and roots, with a slight increase in the concentration of hydrogen peroxide shown both in the roots and in the leaves only for the + Zn variant. In plants grown with the addition of Zn + both chelators, the amount of peroxide formed is similar to that in the control plants or, as can be seen, in the roots at a slightly lower level. The decreased level of hydrogen peroxide in the roots may be related to the fact that the complexed Zn does not contribute to the generation of ROS but perhaps it causes the activation of defense mechanisms. It is unclear whether this is the result of experimental error or a notable trend; confirmation of this requires further research.
CONCLUSIONS

1. The effect of EDTA and NTA on plant growth based on the above data is uncertain. The concentrations of chemicals used in this experiment were likely not enough to elicit a strong effect on the growth of the specimens observed. *Pisum sativum* has been seen to be tolerant of increased Zn levels; therefore higher levels may have been needed for effects to be seen.

2. A much stronger adverse effect was observed in the aboveground parts of the tested plants in the form of the generation of superoxide anion radical and a decrease in the level of photosynthetic pigments. It may be connected with the gradual disintegration of metal-chelator complexes.

3. It is recommended that further research be done with regard to the concentration of EDTA and NTA necessary to elicit a strong effect on *Pisum sativum* var Bohun growth. Additionally, it is recommended that elemental analysis of further specimens be performed via inductively coupled plasma-mass spectrometry (ICP-MS) to accurately determine the Zn uptake for each experimental variant.
About the Authors: Kevin Agner and Michael Larkins

Kevin Agner is a third-year undergraduate student at The University of North Carolina at Chapel Hill. He is from Salisbury, North Carolina, double majoring in Nutrition Science and Music while on the pre-med track. His focus within the music major is cello performance as he participates in chamber music ensembles, solo cello performances and is the principal cellist of the UNC Symphony Orchestra. Kevin became involved with undergraduate research through his colleague, Michael Larkins, a medical student at East Carolina University’s Brody School of Medicine. Kevin and Michael conducted this research project under the advisement of Dr. Aneta Piechalak with the Department of Genome Biology at Adam Mickiewicz University in Poznan, Poland. Their research aimed to explore the use of chelating agents on plants to increase their heavy metal uptake and possibly clean polluted soil.
Comorbidities of Cocaine Addiction and MDD
by Gabriella Keller

Cocaine is one of the most prevalently used illicit substances in the United States, with cocaine addiction commonly occurring alongside Major Depressive Disorder (MDD). Cocaine addiction is formally classified as a disorder in the DSM-V as a substance use disorder (SUD) that can occur comorbidly with MDD. While much is unknown about the origins of these disorders, previous research shows that their underlying mechanisms are more similar than we thought. This paper shows some of the similar mechanisms to include irregular signaling and firing in the ventral-tegmental area, and reduced hippocampal neurogenesis hindering HPA axis functioning. Both of these mechanisms can induce symptoms of cocaine SUD and MDD, and the onset of one disorder may contribute to the development of another by way of changes in neurobiological structures and similar symptoms. The similarities between these disorders illustrate how certain treatment options might be better suited to address comorbid cocaine addiction and MDD, with emphasis on CBT and exercise as non-pharmacological components of treatment.

Keywords: Depression, Cocaine, Plasticity, Hippocampus, Ventral-tegmental area

INTRODUCTION

A national survey conducted in 2016 showed that 1.9 million people were addicted to cocaine in the United States, and in a 2018 survey 5.5 million people reported having used cocaine recently (Thomas, 2020) (NCDAS, 2022). Cocaine is one of the most prevalently abused substances among Americans, and long-term use results in lasting brain damage with negative social and emotional consequences. Cocaine addiction is classified by the DSM-V under the branch of substance use disorders (SUDS), characterized by a patterned use of a substance despite causing distress and impaired functioning (Thomas, 2020). SUDS are commonly comorbid with a wide array of mental illnesses, the most common being Major Depressive Disorder (MDD). The national drug institute reports that among people in the United States seeking treatment for cocaine addiction, 25-61% will experience depressive episodes throughout their lifetime. The comorbidity of cocaine SUD and MDD is mediated by similar underlying mechanisms in both the ventral tegmental area (VTA) and hippocampus, causing maladaptive symptoms and neuronal plasticity (Thomas, 2020) (Nestler, 2005) (Noonan, 2010). Individuals may experience great distress when experiencing these disorders comorbidly, and much is unknown about the origins of these disorders. To treat the millions of people who suffer from SUD and/or MDD, it is worth exploring the neurobiology behind the mechanisms that make these disorders comorbidly occurring.
Background

There are many pathological changes in plasticity to both the VTA and hippocampus when an individual has cocaine SUD and/or MDD. Plasticity is the brain’s ability to alter neural networks, however, SUD and MDD often cause these changes to be pathological and harmful to the individual. One of the main reward circuits I will be discussing is the circuitry that links the prefrontal cortex (PFC), hippocampus, VTA, nucleus accumbens, and amygdala. When parts of these circuits are impaired, they can create a plethora of negative symptoms in the individual and may contribute to the onset and continuation of cocaine SUD and MDD. Both long-term cocaine addiction and MDD can cause pathological firing patterns in the dopaminergic neurons in the VTA (with cell bodies in the VTA projecting into the nucleus accumbens) that exacerbate symptoms of both disorders (Polter, 2013) (Nestler, 2005). This may contribute to individuals experiencing cocaine craving, loss of pleasure in once enjoyed activities, emotional numbness, among other negative symptoms (Gardner, 2011).

Neurogenesis, the proliferation of new neurons and neuronal connections, is significantly impaired in the hippocampus with both cocaine SUD and MDD. The impairment of neurogenesis causes the hippocampus to decrease in volume significantly and renders it unable to function properly. One function of the hippocampus is to inhibit the hypothalamic-pituitary-adrenal (HPA) axis. When it cannot inhibit the HPA axis, there is an increased activation of the stress response (Plotsky, 1998). Both disorders involve a great amount of maladaptive plasticity mediated by the suppression of hippocampal neurogenesis and high levels of stress contributing to their negative symptoms. These disorders may become comorbid in various different ways. For example, during withdrawal from cocaine an individual may feel depressed, lethargic and experience cravings; they are inclined to seek it out to reduce the negative symptoms of withdrawal (Barbosa, 2019; Fung, 1994). In the same respect, individuals who have already been diagnosed with a mood disorder similar to MDD are twice as likely to develop a SUD because they are more prone to seek out cocaine as it counteracts the symptoms of low energy, anhedonia, and depressed mood (Scofield, 2009).

There are effective treatments available to help those who have both of these disorders, and there are overlapping treatments that may be useful in treating comorbid cases. Cocaine SUD treatment options may include cognitive behavioral therapy (CBT) and exercise. Treatments for MDD include a wide variety of psychotherapy options such as CBT, exercise, and antidepressant medication, most notably SSRIs (Eisch, 2008; Micheli, 2018). CBT has been found to improve VTA signaling to the amygdala, hippocampus and various other regions that it projects to. SSRIs along with exercise have been shown to improve hippocampal neurogenesis (Collerton, 2013; Rounsaville, 2004). These disorders have a significant impact on the quality of life for those who are struggling with them, but the treatments available may greatly reduce negative symptoms and give individuals the tools that they need to cope with them.

Cocaine Substance Use Disorder

Signaling in the VTA with Cocaine Use

The mesolimbic dopamine system is one of the major pathways of the brain known for its role in reinforcement, motivation and drug-seeking behavior. Many drugs of abuse, including cocaine, affect the dopaminergic receptors in the ventral-tegmental-area (VTA) and their axons extend into the nucleus accumbens & amygdala (Nestler, 2005). Certain neurons have cell bodies in the VTA and project into the nucleus accumbens. When these neurons are stimulated, dopamine is released into the nucleus accumbens. Cocaine blocks the dopamine transporters in the nucleus accumbens, causing an accumulation of dopamine in the synaptic cleft to overstimulate the dopaminergic receptors (Wolf, 2016). The increased rate of firing due to the extra dopamine changes the neural connections, and plasticity of the neurons allows for adaptations to occur in the mesolimbic dopamine system that are pathological (Nestler, 2005). These pathological changes induce drug-seeking behavior, where an individual learns to associate cocaine with positive effects (Thomas, 2008). Pathological changes are most often seen when the influx of dopamine causes motivational cues to become oriented to cocaine, changing behavior in a way that increasingly leads the individual to seek out and use the drug more frequently (Mahoney, 2018; Nestler, 2005).

During long-term cocaine use, dopaminergic neurons fire stimulating dopamine release in response to drug or drug related cues, resulting in drug seeking behavior. This happens primarily when an individual is anticipating a reward, and the stimulation of dopaminergic receptors motivates them to seek out the reward (Wolf, 2016). This
reward seeking behavior stimulated by the release of dopamine in anticipation of the drug is one of the primary causes of cocaine addiction (Nestler, 2005). When an individual is expecting cocaine and does not receive it, the dopaminergic receptors fire at a decreased rate inducing feelings of depression and craving. This decreased firing occurs extensively during withdrawal; causing high rates of relapse and fueling addiction (Nestler, 2005; Mahoney, 2018).

Impairment of Hippocampal Neurogenesis from Cocaine Use

Neurogenesis in the hippocampus is an important part of healthy functioning because new neuronal connections are formed from memory making and learning (Abrous, 2005). Impaired proliferation of new neurons in the hippocampus is associated with cognitive impairments and increased stress, and the neurons that are already present become atrophied (Boku, 2018). The neurogenesis hypothesis states that impairment in making new neuronal connections contributes to maladaptive behavioral changes that may mediate drug use. A study conducted on mice showed that artificial suppression of hippocampal neurogenesis led to a direct increase in cocaine self-administration, establishing the link between hippocampal neurogenesis and susceptibility to addiction (Noonan, 2010). When neurogenesis is functioning properly in the hippocampus, it can protect against cocaine primed-relapse by way of the hypothalamic-pituitary-adrenal (HPA) axis (Eisch, 2008).

The HPA axis mediates the stress response in our brain, and the hippocampus is the main inhibitor of the axis (Abrous, 2005). When the hippocampal neurons become atrophied and neuronal proliferation is not occurring, the hippocampus cannot inhibit the HPA axis easily and therefore the stress response activates more often than it should (Plotsky, 1998; Boku, 2018). With the HPA axis uninhibited, the adrenal cortex releases much more cortisol than usual in situations where there is no apparent stressor and no reason for this type of signaling to be occurring (Abrous, 2005). This increased stress response causes a surge in the corticosteroids circulating in the system, and individuals may try taking more of the drug to lessen the stress that they are feeling, fueling their addiction (Chambers, 2013). Impairment of hippocampal neurogenesis causes a cycle where increased stress influences drug-seeking behaviors that further atrophy the neurons already present, making it difficult to stop using cocaine (Eisch, 2008; Boku, 2018).

Major Depressive Disorder VTA Dopaminergic Firing Patterns

Abnormalities in VTA dopamine neurons lead to changes in the plasticity of the mesolimbic system by way of dopaminergic projections to the nucleus accumbens and medial prefrontal cortices. Inappropriate mesolimbic dopamine firing patterns can lead to the reinforcement of maladaptive behaviors and increased negative feelings associated with depression such as anhedonia, aversion, and depressed mood. Malfunction of the brains reward circuitry, particularly in the VTA, greatly mediates the stress-induced behaviors present in depression including social defeat and aversion (Lammel, 2014). Inappropriate dopamine firing is seen in individuals with depression, particularly in a burst pattern of firing after aversive and stressful events (Polter, 2014; Chaudhury, 2013).

The spontaneous and burst firing patterns of dopaminergic neurons from the VTA projections can also happen after instances of social defeat and aversion, leading to the conclusion that these depressive symptoms are changing the firing patterns in the VTA in a maladaptive way (Chaudhury, 2013). These changes in the firing patterns are changes in plasticity that ultimately reinforce the negative symptoms and leave the individual in a positive feedback loop and unable to stop their depressive symptoms. This is one of the main mechanisms that many negative symptoms associated with depression are mediated by, since firing patterns over time seem to become more associated with stress-related cues. This is theorized to be contributing to depressed mood, anhedonia, and lethargy (Thomas, 2008). The inappropriate dopaminergic firing pattern seen in individuals with depressed behavior and chronic stress returns to normal firing after individuals have taken SSRIs (antidepressants) (Polter, 2014).

Impairment of Hippocampal Neurogenesis Mediates MDD

Impairment of neurogenesis is a symptom of MDD that leads to the inability to generate new neurons in the post hippocampal dentate gyrus. PET and fMRI scans of depressed patients show that the hippocampus is decreased in size.
compared to non-depressed patients, which can further mediate depressive symptoms. When the hippocampus is atrophied it can no longer inhibit the HPA axis effectively, leading to elevated levels of corticosteroids circulating in the system (Plotsky, 1998; Abrous, 2005). Elevated corticosteroids levels cause dendritic arbors in the hippocampus to shrink, causing further deficiencies in the inhibition of the HPA axis (Eisch, 2008). This positive feedback loop is a contributing factor to why depression left untreated often does not go away on its own, and why treatment early on is so important (Plotsky, 1998).

Neurogenesis in the hippocampus is increased when a depressed patient is taking antidepressants and is decreased when they are not, making it an effective aspect of treatment (Hill, 2015). The hippocampus is crucial for consolidation of long-term memory, episodic memory, and spatial navigation, and these types of memory heavily influence the ability to consolidate new memories (Peroza, 2020). The loss of hippocampal neurogenesis impairs learning and memory in depressed patients, contributing to the short-term memory loss seen in individuals with MDD. This is also why two major symptoms of depression reported in patients is forgetfulness and confusion (Eisch, 2008).

Suppression of hippocampal activity in the hippocampus affects the areas that its neurons project to, the most notable being the medial prefrontal cortex (Plotsky, 1998). The decreased activity in this area is associated with impaired hippocampal-dependent cognition which can cause problems with decision making and judgment (Eisch, 2008; Peroza, 2020).

Hippocampal Neurogenesis in Comorbidity

Suppression of hippocampal neurogenesis in both cocaine SUD and MDD make these disorders highly comorbid and greatly influence how these disorders are mediated by common abnormalities (Eisch, 2008). The hippocampus is crucial for inhibiting the stress response mediated by the HPA axis, leading to high levels of stress reported in individuals suffering from both disorders (Plotsky, 1998; Eisch, 2008). An individual suffering from a mood disorder such as MDD is twice as likely to abuse substances than an individual who is not, and this is an important factor when considering why these disorders are so often comorbid (Thomas, 2008). In individuals with MDD presenting first, the lack of hippocampal neurogenesis inducing higher levels of stress may lead them to attempt self-medication with cocaine, leading to a substance use disorder (Polter, 2014). In individuals who originally present with cocaine SUD, the higher levels of stress may be a contributing factor to the onset of an episode of MDD, especially during an untreated period of withdrawal where depressive symptoms are maladaptively because they are firing to drug or drug related cues, and in MDD they are firing in abnormal burst patterns to stress-related cues. The changes in the VTA synapses from acute stress related to depression parallel the changes seen from addictive drugs, meaning that there is a common mechanism at work that contributes to a greater chance of comorbidity. This becomes especially important when looking at the symptoms experienced by individuals going through withdrawal from cocaine (Polter, 2014).

Cocaine withdrawal induces a variety of negative symptoms that may contribute to a diagnosis of comorbid cocaine SUD and MDD (Mahoney, 2018). Similar to symptoms of MDD, cocaine withdrawal symptoms may include depressed mood, difficulty concentrating, as well as disturbances in appetite and sleep. Withdrawal symptoms in substance use disorders are mediated by drug cue induced responses in areas of the brain that the VTA has dopaminergic projections to (Polter, 2014). A study conducted by McClernon et. al reported that drug craving went up significantly during withdrawal, and abstinence induced cravings were positively correlated with drug-related cues (McClernon, 2005; Mahoney, 2018).
commonly reported (Mahoney, 2018). The ability of the hippocampus to inhibit the stress response is vital for reducing negative symptoms associated with both disorders (Eisch, 2008; Chambers, 2013).

Treatment of Comorbid Cocaine SUD and MDD

**Non-pharmacological Treatment**

Cognitive behavioral therapy (CBT) can be an effective treatment for decreasing the hyperactivity in the limbic system seen in both MDD and cocaine SUD. CBT decreases activity particularly in the amygdala, one of the major areas of the brain that the VTA projects to (Collerton, 2013). The amygdala is crucial in processing negative emotions and has projections to the hippocampus that send key information about whether it needs to inhibit or express the stress response via the HPA axis (Plotsky, 1998; Eisch, 2008). This is especially important because activity in the amygdala is heightened in patients with MDD & SUD, and CBT can effectively reduce the hyperactivity in this area. The mechanisms with which CBT does this is largely unknown, although it is thought to change the way that individuals process emotion-relevant information by altering maladaptive patterns of thinking (Collerton, 2013).

Exercise has been shown to increase hippocampal neurogenesis, and after 3 days of voluntary running there is a significant increase in the proliferation of neurons. In addition to increasing hippocampal neurogenesis, exercise also increases performance on various hippocampus-dependent cognitive tasks, especially ones involving spatial memory. Running has been found to directly reduce depression-like symptoms, however only an SSRI has been found to reduce the overwhelmingly reported symptom of anhedonia in individuals with MDD (Micheli, 2018).

**Psychopharmacological Treatment**

In cases where cocaine SUD is occurring comorbidly with MDD, selective serotonin reuptake inhibitors (SSRIs) can be an effective treatment for MDD. In some cases, SSRIs may even improve a comorbidly occurring SUD. SSRI treatment can activate adult neurogenesis in the hippocampus, which is one of the key mechanisms for treatment in both disorders. The SSRI fluoxetine shows a slight increase in proliferation of neurons in the hippocampus after 5 days and a significant increase after 7 days; a critical component of decreasing the hyperactive HPA-axis (Micheli, 2018) (Boku, 2018; Plotsky, 1998). If the hippocampal neurogenesis occurs and the hippocampus can effectively inhibit the HPA axis, then the stress response activates less frequently and corticosteroid levels decrease (Eische, 2008). Patients with MDD and/or cocaine SUD have much higher corticosteroid levels than patients with no MDD/SUD diagnosis, so individuals may feel relief from some of their symptoms through methods that increase neurogenesis (Plotsky, 1998).

There is conflicting evidence on whether fluoxetine affects cognitive behavior. It has not been found to increase performance on memory-dependent tasks, and in humans has been found to cause impairments in episodic memory (Wadsworth, 2005). Cocaine use has been found to cause cognitive impairments, especially interference with episodic memory, so SSRIs may not be useful for some patients with cocaine SUD (Mahoney, 2018) (Vonmoos, 2014). SSRIs have been found to have some negative side effects; they have not been found to impair functioning and have been found to improve the quality of life for those who are suffering from these disorders (Micheli, 2018).

The combined treatment of SSRIs, CBT, and exercise can help to combat impairments in memory experienced in individuals taking only SSRIs. These three types of treatment, when used together, can provide extensive relief from the negative symptoms that individuals may be experiencing (Rounsaville, 2004).
References


My name is Gabriella Keller and I'm a senior from Winston-Salem, North Carolina. I'm a Psychology major with a minor in Neuroscience, and planning on going to graduate school for Clinical Psychology after taking a gap year to gain research experience in post-baccalaureate positions. Some topics I'm passionate about exploring in the future include psychopathology, substance use, and positive psychology. I first became interested in researching substance use after taking a freshman seminar on drug addiction with Dr. Reissner, and I joined her lab as a research assistant to pursue this passion. The Reissner lab studies how glial cells in animal models are affected by cocaine use, and this was the inspiration for my paper. After my experience learning about substance use through animal models, I wanted to gain experience working with human subjects. I currently work in the Positive Emotion and Psychophysiology (PEP) lab under Dr. Fredrickson and am completing another independent research course in social psychology. The PEP lab has many ongoing projects studying different aspects of positive psychology, and my most recent project is on positivity resonance in romantic partnerships. In my free time I like watching thriller movies, playing chess, and spending time in nature.
The Americanization of Manga: How Japanese Graphic Novels Are Redefining Literary Genres

By Luke Morton

In this paper, I will argue that graphic novels, namely manga, have begun to surface as a staple genre of our time, largely in part to their recent increase in literary prominence in America and their compatibility with the modern age. I will support this by looking at the current popularity of the genre and the increasing demand for it both globally and domestically, followed by how it serves as a medium for combining art and literature not found in other traditional forms supported by the work of Jane Baetens and Hugo Fry. Next, I will point to the blending of genres that gives manga a seemingly endless range of possible stories which simultaneously fuel this unique potential to blend genres. Finally, by first observing Paul Lopes’ findings on the stigmas facing the more familiar American comic, I will discuss the stigmas and preconceived notions that have halted the genre’s movement into Western spheres and previously prevented its solidification as a format rich with literary value and significance.

Keywords: Graphic Novels, Genres, Manga, Art, Literature

We live in a world full of constant change that is marked by an increasingly fast-paced way of life. With this shift in global culture, consumers need the products they purchase to fit into this rapid lifestyle. In recent years the popularity of graphic novels has skyrocketed nationally pushing the emerging genre towards the front of public consciousness and sparking debate about this previously dismissed format’s literary value. So, how could a genre that is often considered to be strictly for little kids or people refusing to grow up have the potential to usher in a new age of literature fit for our fast-moving technological world while sparking literary interest across genres in new readers?

The global pandemic played a key role in launching the already growing North American manga market to new all-time highs in 2020. Throughout the pandemic anime, animated television adaptations of manga showed an enormous increase in streaming hours on services such as Funimation and Netflix. The anime adaptation of Attack on Titan was the most-watched show in the United States from January 31 to February 6 with an audience demand among American viewers that was 46% higher than in Japan (Parrot Analytics, 2021). The film adaptation of Demon Slayer’s “Mugen Train Arc” broke multiple global records this year by becoming the highest-grossing anime film of all time with a global box office revenue of four hundred and forty million dollars and a profit of forty-five million in American theaters, outselling films like House of Gucci and Wonder Woman 1984. (Butler, 2021 & Brady, 2021; Box Office Mojo, 2021). This played a prominent role in the series’ manga finishing second in sales worldwide so far this year (Ashcraft, 2021). This trend continues across the board and consequently
drove manga sales to nearly two-hundred and fifty million dollars in North American markets compared to the previous high of about fifty million in 2007 (Griepp 2021). These statistics help express how manga's Japanese roots have reached far past their native shores and that the genre has begun to establish itself as a cornerstone of American pop-culture and media, regardless of whatever literary value one considers it to have.

Manga is a literary format truly inseparable from its art. While reading a manga volume the reader is fully connected to the story through a continuous visual immersion that other modes of literature are unable to replicate. Whether it's over twenty years of world-

building in One Piece, the complex philosophical dilemmas of Neon Genesis Evangelion, or the sweeping landscapes of Berserk the reader is presented with the narrative's physical world and characters along with its metaphysical aspects like inner thought simultaneously in a way unique to manga. Therefore, the reader can form a deeper connection with the narrative since this holistic picture of the author's, or in this case, the mangaka's, work allows them to grasp the deeper meanings and lessons behind what they are reading.

This mutually exclusive mixture of art and literature that defines the genre provides visual immersion for the reader, but skillful authors also toy with it in ways that add to the audience's literary experience. This is demonstrated by how Masashi Kishimoto, the mangaka of Naruto, uses an artistic parallel between the series' protagonist, Naruto, and his foil, Sasuke, to make a literary parallel between them at the same time. These panels take place hundreds of chapters apart and show how these two characters, both essential to and closely followed by the story, have been given two extremely different outlooks on the same village due to how their differing experiences have shaped their perspectives on pain and revenge. Manga is typically released in weekly volumes or monthly chapters since the mangakas are following a tradition of putting time and care into their artwork that goes back to the twelfth century. This release schedule further connects the reader to the narrative since they are given a more satisfying and meaningful delayed gratification by making them wait each week or month to find out what happens next compared to the instant gratification of binge-watching a Netflix show that may tell a similar story. Series such as Naruto have been around for decades and their progressive release spans over meaningful moments of readers' lives and even helps some through difficult times, causing them to associate these characters' development with feelings of nostalgia as they grow with them.

With the idea of anime content in the metaverse already being considered by the studio behind Pokémon, some passionate about the genre have raised concerns that increased digitalization may cause it to lose some of the human aspect crucial to it. However, Jane Baetens and Hugo Frey, two scholars whose work concerns graphic novels, say in their description of graphic novels as a specific mode of storytelling, “But we maintain that a story in graphic novel format is more than just a story told in graphic novel format: the choice of the medium induces a set of possibilities as well as impossibilities, of obstacles as well as chances, that are not found in other media, even if it remains always possible to retell or remake a given story in a different medium” (Baetens and Frey 2014). These sentiments about how the mixture of art and literature and the human tradition behind it make the genre what it is all still hold true when a manga volume is read in a digital format. Technological elements such as digital art tools have allowed mangaka like Jujutsu Kaisen's Gege Akutami to master the fluidity of human motion or One Punch Man's Yusuke Murata to add sleek finishes to his panels.

Crunchyroll, arguably the most prominent anime-
specific streaming service, has a popular page that ranges from typical stories about becoming the world’s strongest hero, such as My Hero Academia, to shows literally about being reincarnated as a slime. The genre’s vast potential for genre building is also related to the format’s unique way of connecting to the reader’s own lives as new mangakas have begun to emerge and blend aspects of the series that influenced them growing up. The author of Chainsaw Man, Tatsuki Fujimoto was quoted as saying, “If I tried to depict hell without thinking about it, it would end up like “The Eclipse” from Berserk”, in an introductory note in a volume of his hit series following the passing of Kentaro Miura, mangaka of the previously mentioned Berserk.

Berserk is widely considered to be the definitive manga of the Seinen subgenre, and it serves as a prime example of manga’s unique way of influencing future works. Fujimoto’s testament to Miura’s work may sound like him resenting the famous author for his childhood nightmares, however, Chainsaw Man revolves around the concept of devils from its universe’s version of hell and as shown above Miura’s fondness for blood and gore certainly rubbed off on Fujimoto.

The genre has enjoyed popularity throughout the Eastern world for much of its history and even reached European audiences before starting to take hold in America to finish its globalization as a hallmark genre of the twenty-first century. In reference to America’s particular hesitancy to embrace the graphic novel, comic book scholar Paul Lopes attests, “In reading histories, interviews, columns, and other writings in the subculture of comic books, I found the multiple levels of stigma to be quite remarkable” (Lopes 2006). These typical stigmas Lopes mentions such as being considered to have strange or immature subject matter or holding no real literary value apply just as much if not even more so to manga. Comic books are distinctly American, giving them a sense of familiarity among Western readers which manga is denied due to its Japanese origins. Traditional American comic books only started being produced in 1938 and as previously mentioned Japanese manga can be traced back centuries (Kowalski 2021). This age difference seems to refute the idea that manga is something new and strange compared to traditional comic books and leaves one to wonder if these sentiments could ultimately stem from subconscious xenophobia or racism. As previously mentioned, this is far from the case in the present day with manga and graphic novels reaching such popularity that even Disney recently released Star Wars: Visions, an anime skit series, in an apparent attempt to test their potential in the anime and manga markets.

Change and adaptation seem to be going nowhere as the world adjusts to a new normal. In a world revolving around these qualities, manga and graphic novels seem to be perfectly fit to provide literary fulfillment to a new generation of readers growing up in this ever-changing environment. As the world becomes more experience-based and the genre continues to shape this century’s literary tradition, how else will the genre evolve with technology and further capitalize on its unique method of storytelling to challenge our idea of what literature can truly be?
Works Cited


I am a first-year student from Raleigh currently majoring in English on a pre-law track. I have always loved the art of storytelling and have found myself attracted to different forms of literature all my life. Ever since I was young I have been fascinated with graphic novels, always taking trips to the comic bookstore with my dad or reading manga online. Throughout much of my life I have tried to suggest different graphics novels or TV adaptations to friends and family with little success, until recently when the concept of manga and anime have seemed to reach a certain level of social acceptance online. Last semester I took Intro to Popular Genres with Professor Shand where we discussed how different physical forms can affect how a story can be told in that format, particularly when discussing the history of broadside ballads. For my final research paper in the class, I considered how graphic novels, particularly Japanese manga, hold value as a literary genre by looking at their rapidly growing popularity and unique potential to mix art and literature, inspired by the previously mentioned broadside ballads. This also led me to consider the reasons the genre has failed to gain popularity as quickly in Western spheres as it did elsewhere globally which I touch upon in the essay.
In contrast to the strongly teleological, goal-directed nature of Western art music, the musical style of minimalism has long been purported to be antiteleological—that is, it lacks the logical “musical argument” found in traditional teleological music. Robert Fink, however, has asserted that minimalism is indeed goal-directed but through “one-piece, multiple climaxes” recombinant—as opposed to “one piece, one climax” classical—teleologies. As these concepts pertain to Philip Glass’s piano etudes, most all of them demonstrate the recombinant teleologies described above, as there is no specific text Glass is trying to interpret and thus no specific narrative requiring the invocation of classical teleologies. However, Etude No. 6 is a striking outlier in that he is tasked with interpreting the text of John Ashbery’s poem, No Longer Very Clear. In order to do so, I argue Etude No. 6 psychologically manipulates texture and meter through the variation and rondo strategies proposed by David Huron (as opposed to traditional manipulations of thematic material, key areas, dynamics, etc.) as a means of interpreting Ashbery’s text through the context of a dream, an inherently symmetrical phenomenon in which stages 1-4 of the sleep cycle gradually decrease one’s consciousness, leading to REM sleep that is followed by a gradual restoration of consciousness. As such, this paper seeks to demonstrate how Glass’s Etude No. 6 builds on Fink’s argument, illustrating how the form of a minimalist work can be psychologically “maximized” so as to unconventionally recreate classical teleologies in the service of conveying narrative.

Keywords: music theory, music cognition, music psychology, music analysis, minimalism
INTRODUCTION

In the late 1960s, after decades of seemingly arcane serialism, Philip Glass and several other composers—including Steve Reich, Terry Riley, and La Monte Young—revolted against what they perceived to be the academic musical establishment, stripping music down to predominantly consonant harmonies, steady pulses, and persistent repetition. As such, it has widely been said that minimalism is ‘antiteleological’ in that it lacks what Belgian musicologist Wim Mertens describes as the goal-directed, logical “musical argument” that he argues is characteristic of traditional Western art music. (1) In a 1980 study of the new American minimalist movement, Mertens describes the difference between Western classical music and minimalism in the following way:

Traditional dialectical music is representational: the musical form relates to an expressive content and is a means of creating a growing tension; this is what is usually called the “musical argument.” But repetitive music is not built around such an “argument”; the work is non-representational and is no longer a medium for the expression of subjective feelings. (2)

In other words, Mertens defines what he refers to as “dialectical” music as being based on a logical flow of musical ideas and arguments, whereas “repetitive” music is not. Yet what Mertens fails to consider is that even the absence of such clear-cut ideas and arguments could be read as expressively significant in the classic representational sense as, for example, a “life in stasis.” Nevertheless, Mertens is certainly not alone in expressing such sentiments. In Steve Reich’s widely-read 1968 essay, “Music as a Gradual Process,” he argues that music should be an audible yet impersonal process. (4) Decades later, Philip Glass echoed similar thoughts of his desire for music to remain as objective as possible in a 2009 interview with Tim Page. In this interview and with regards to his own music, Glass claimed that,

The listener will therefore need a different approach to listening, without the traditional concepts of recollection and anticipation. Music must be listened to as a pure sound-event, an act without any dramatic structure. (5)

That being said, the fact of the matter is that there is no way to create 100% objectivity from the listener’s perspective, as each listener will bring their own unique sets of associations attached to genres of music that will necessarily affect the expressive connotations of the “gradual processes” Reich and Glass allude to above. In other words, each listener will bring their own unique listening experiences to a given performance and they cannot simply disregard what they’ve already learned through experience, thus undermining Glass’s goal of musical objectivity.

As these ideas pertain specifically to his etudes, in the foreword of Glass’s The Complete Piano Etudes, he claims that he wrote his etudes with the sole intention of improving his piano technique. In other words, his only goal was for them to be pedagogical exercises—nothing more, nothing less. For the most part, this seems to be quite clear: in almost every single etude, there seems to be an exclusive emphasis on technical challenges for the pianist. Shifts in harmony, texture, and meter do not seem to follow a clear trajectory but rather tend to create multiple small-scale build-ups that lead to numerous climaxes of hierarchical equivalence. For example, in Etude No. 13, the first two subsections of (a) and (b) grow in textural density and vary in levels of metrical consonance and dissonance, thus leading to a “climactic” third subsection of (c). However, this same build-up repeats two more times in mm. 17-44 and 45-60, thus undermining any sense of a singular, paramount climax. A similar instance of multiple hierarchically equivalent climaxes can be observed in Etude No. 1, where subsections 5-10 (mm. 18-41) grow in texture and vary in levels of metrical dissonance, leading to “climactic” subsections 12-14 (mm. 42-61) and this same build-up recurs again in mm. 62-90 and 91-105.

Where Glass departs from this apparent norm, however, is in Etude No. 6, where he was

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2 Ibid.
3 For a general consensus on the historical view of minimalism as ‘antiteleological’ throughout music scholarship, see Beirens (2003), Bonds (2013), Burkholder et al. (2019), and Reich (2018).
the in 1994 to set the text of John Ashbery’s poem, “No Longer Very Clear”:

It is true I can no longer remember very well
the time when we first began to know each other.
However, I do remember very well
the first time we met. You walked in sunlight,
holding a daisy. You said, “Children make unreliable
witnesses.”

Now, so long after that time,
I keep the spirit of it throbbing still.
The ideas are still the same, and they expand
to fill vast, antique cubes.

My daughter was reading one just the other day.
She said, “How like pellucid status, Daddy. Or like a...
an engine.”

In this house of blues the cold creeps stealthily open us.
I do not dare to do what I fantasize doing.
With time the blue congeals into roomlike purple
that takes the shape of alcoves, landings...
Everything is like something else.
I should have waited before I learned this. (6)

Thus, whether or not Glass intended to invoke a so-called “extramusical” meaning to this etude, the relation to a specific poetic text is likely to strongly influence the listener’s interpretation of the etude.

Taken at face value, Ashbery’s poetic text is decidedly abstract, creating a sense of stasis. Yet this text holds a far deeper latent meaning that is not revealed until the very last line, “I should have waited before I learned this,” indicating the narrator has just woken up. In other words, what initially appeared to be a static memory of the narrator’s past was actually a reliving of their past in the context of a dream, which is an inherently symmetrical, goal-directed process. As we will see, in order to go about conveying this dream-based interpretation musically, I argue Etude No. 6 meticulously employs various repetition-based psychological formal strategies (to use David Huron’s conceptualization of the term).

In Huron’s essay, “A Psychological Approach to Musical Form: The Habituation Fluency Theory of Repetition,” he makes it clear that the empirical research he conducted was solely based on exact-and non-exact repetition, including a variety of world musics—Calypso music, Inuit throat singing, Japanese New Age, Estonian bagpipe, Punjabi pop, Navaho war dances, Ghanaian drumming, Spanish Flamenco, Hawaiian slack key, Kalimantan ritual music, North African Berber music; Macedonian, Tuvian, Turkish, and Ugandan musics—and thus by no means limited to traditional Western classical forms. (7) Accordingly, the concepts he proposes are intentionally left broad and thus are potentially applicable to any form of music that employs them. The two types of strategies that Etude No. 6 meticulously employs include the variation strategy—that is, when a passage features slight yet persistent modifications, and the rondo strategy—that is, subverting habituation by introducing novel materials at crucial points and shortening later repetition cycles to offset the potentiation of habituation. (8) As Huron notes, the variation and rondo strategies he describes are based solely on subtle changes in repetition in contrast to more traditional manipulations of formal functions, thematic material, key areas, dynamics, and so forth that one finds in Western classical music. He further notes that the degree of variability in minimalism is quite “minimal,” limiting its ability to make the best use of these psychological strategies. (9) Thus, the unique adaptation of these psychological strategies in Etude No. 6 is an outlier for Glass not only in the fact that he uses them but also in how they are meticulously manipulated in such a way that allows for the unconventional creation of a dream-based narrative. As alluded to earlier, while it might initially seem ironic that Glass chose to engage such a goal-directed narrative to set a seemingly non-linear text, the last line of the poem (“I should have waited before I learned this”) reveals the latent dream reading of the text.

In Robert Fink’s Repeating Ourselves: American Minimalism as Cultural Practice, he refutes the long-held discourse distinguishing the so-called “goal-directed,” “teleological” nature of Western classical and pop-rock music from the purported “antiteleological” nature of minimalism, disco, and non-Western musics. Instead, Fink argues there is a more nuanced distinction found between classical teleologies of the former and recombinant teleologies of the latter. In other words, while the classical teleologies of Western art music contain multiple tension-release arcs, they are embedded hierarchically such that they are structured around
One might question Glass's rationale for going to the effort of using these psychological strategies in such a large-scale, goal-directed fashion that seems to defy the norm of recombinant teleologies used in his other etudes that do not appear to follow such a trajectory. While determining compositional intentions is not at all the goal of this analysis, I argue that Glass's setting seems to interpret Ashbery's text through the context of a dream, and sleep is an inherently symmetrical, goal-directed activity. In other words, while dreams are inherently abstract and lack any sense of goal-directed trajectory, the underlying physiological mechanisms of sleep are inherently goal-directed (i.e., to restore energy, repair tissues, etc.). In this sense, abstract dreams (in this case, Ashbery's literal text) coincide latently with the inherently goal-directed process of sleep. Our state of unconsciousness increasingly heightens until we reach a "climax" of REM sleep, and then we progressively restore our consciousness as we wake up. Thus, the goal-directed psychological nature of sleep itself creates a sort of symmetry in our levels of consciousness. In the sleep cycle, Stage 1 consists of mere drowsiness with an overall loss of awareness, thought, and responsiveness, Stage 2 consists of deeper sleep than Stage 1, Stage 3 consists of even deeper sleep than Stage 2, Stage 4 contains the deepest pre-REM sleep yet, and finally, Stage 5 consists of rapid-eye-movement (REM) sleep in which the body is paralyzed and dreams flourish. As such, we can interpret the A section's increasing levels of textural density and metrical dissonance as the dreamer's state of mind as they fall asleep, the B section's prolonged textural density and metrical dissonance as REM sleep itself, and the A' section's decreasing levels of textural density and metrical dissonance as the dreamer's state of mind as they start to gradually wake up.

On the macro-level of form, and as alluded to above, this work seems to follow a formal structure of ABA'. To create the aforementioned symmetry, Glass invokes a symmetrical design among the subsections, creating a figure 6 and 7 units of the B section are both material we have not yet heard up until one single climax. In contrast, Fink claims that recombinant teleologies abandon the "one piece, one climax" teleology that is characteristic of Western art music, and instead these teleologies are derived from multiple hierarchically equivalent tension-release arcs, works where tension-release arcs occupy only some of the parameters, works with nothing but climaxes, etc. (10) While such recombinant teleologies are certainly applicable to Glass's other etudes, I argue that Etude No. 6 inextricably links psychological formal strategies and narrative in such a way that more closely resembles classical teleologies, with an accumulative build-up of the A section leading to a single "climactic" B section followed by a decumulative A' section. Thus, Etude No. 6 manipulates the conventional approach taken to classical teleologies via the psychological strategies it employs. Unlike traditional classical teleologies such as sonata form in which a singular, paramount climax is generated through unconventional harmonies, key areas, and dynamics, this etude's reliance on the variation and rondo strategies creates a paramount climax through varying levels of textural density and metrical dissonance. In this sense, Etude No. 6 has reinvented how scholars have historically conceptualized the "classical" teleology described by Fink. Figure 1.2 illustrates how this etude uses Huron's strategies to psychologically manipulate how the "one piece, one climax" structure is traditionally constructed in sonata form seen in Figure 1.1.

![Figure 1.1.](chart1.png) Figure 1.1. A chart illustrating traditional "classical" teleologies in sonata form.

![Figure 1.2.](chart2.png) Figure 1.2. A chart illustrating how Etude No. 6 uses an unconventional psychological approach to manipulate traditional "classical" teleologies while still creating the same trajectory.
creates what I would describe as *decumulative form*—that is, the inverse of accumulative form, in which a groove gradually breaks down into its constituent parts.

Second, Glass manipulates meter through varying degrees of metrical consonance and dissonance (12) (as conceptualized by Krebs) in the work. As a result of these metric shifts from one subsection to another, Etude No. 6 manipulates the listener’s in-time metric perception by constantly altering projective and projected potentials (13) (to use Christopher Hasty’s terms) and thus the listener’s metrical entrainment (14) (to use Justin London’s term). Thus, as we will see in the forthcoming analysis, the A section “accumulates” not only texture but also increasing levels of metrical dissonance, in keeping with the variation strategy; the B section creates “climax” not only through elongated textural density but also through prolonged periods of extreme metrical dissonance, in keeping with the rondo strategy; and finally, the A’ section “decumulates” not only by decreasing levels of textural density but also by degrees of metrical dissonance, returning to a state of metrical consonance by the final subsection of (a), in keeping with the variation strategy. In what follows, I seek to analyze each section and subsection of Etude No. 6 in greater detail to illustrate how its scrupulous use of psychological strategies described by Huron manifest themselves into a clear narrative, thus defying the purported ‘antiteleological’ view of minimalism and further demonstrating how these psychological strategies can be used towards an unconventional means in minimalism.

Glass’s Usage of the Variation Strategy in the Introduction and A Section

As alluded to above, Huron defines the variation strategy as the repetition of a given passage with slight modifications upon each iteration. This strategy hinges itself on the phenomenon known as *stimulus generalization*, or the subverting of habituation due to minor changes in repeated material while simultaneously using similar material to benefit from the positive feelings created by processing fluency. (15) In other words, repetition can be both a positive attribute via processing fluency and a negative attribute due to habituation, so the variation strategy strikes a balance between the two and keeps the listener engaged by allowing for the minimalizing of...
bodies become paralyzed and thus our senses becoming increasingly shut off from reality. Thus the “alignment” of our senses with reality becomes increasingly nonaligned in the same way that metrical dissonance refers to the “nonalignment” of interpretive metrical layers. Measure 6 is crucial in that it is the first to establish two groupings of 6 due to the harmonic shift from $\flat V7$ to $V6/5$ halfway through the bar, creating a phenomenal accent ($16$) that results in a consonance of $6/2$. Thus, from this regular occurrence of two groupings of 6, it is reasonable to assume that the listener will begin to feel (and perhaps become entrained to expect to feel) each measure in this same compound duple grouping. In other words, in m. 6, the dotted half note’s projected potential as the newly felt sound event is realized for its relative determinacy as a projective potential on the seventh eighth note of the measure. However, as we will see, Glass’s set-up of this expectation allows him to maximize the variation strategy in future subsections where this projected potential will increasingly become shifted or denied altogether.

In the introduction, Glass establishes the eighth note as the underlying pulse layer but leaves the meter ambiguous in terms of higher interpretive layers, creating a sense of neutrality that represents objective reality. In other words, at this point the dreamer has yet to fall asleep; Glass is simply setting a “baseline,” non-dream state of consciousness. As we will see in the A section, however, higher interpretive layers of meter will eventually be suggested, creating both 2-beat cycles (two dotted half notes per bar) and 3-beat cycles (three half notes per bar). Thus, one could say that this “objective” left-hand reality is in the process of becoming—its malleability will allow for Glass to vary both the texture and meter as a means of invoking the variation strategy.

In (a), the introduction of the right hand—though limited mostly to repeating F4 eighth notes—creates a denser texture from what we’ve heard so far. Thus, at this point we can visualize that the dreamer has entered a drowsy Stage 1 of the sleep cycle—they are still conscious, but simply less cognizant of their surroundings. Accordingly, (a) reinforces the eighth-note pulse layer first established in the introduction. In this sense, metrical consonance is synonymous with psychological consciousness, as the alignment of interpretive layers coincides with the alignment of one’s senses with reality that ceases to exist in REM sleep. In other words, in keeping with Krebs’s definition of metrical consonance as the maximal “alignment” of all layers of motion, when we are conscious, our senses are in touch with or “aligned” with objective reality, but as we fall asleep, our

In (b), Glass upholds the processing fluency aspect of the variation strategy by presenting the same exact bassline, harmonic progression, and rhythmic figures heard in (a). At the same time, however, in order to circumvent habituation and illustrate the first signs of unconsciousness that are characteristic of Stage 2 of the sleep cycle, he includes slight modifications in both the left and right hands. In m. 7, we begin with a carryover of two groupings of 6 in m. 7, as if one is to view the G4s on the third beat of the measure as a passing tone, the Ab4 creates a phenomenal accent due to the fact that it is part of the underlying F minor harmony in the left hand. In m. 8, however, the left-hand eighth notes shift to groupings of 4 per measure due to the Bb4 on beats 2, 4, and 6, changing the sonority from D-flat major to Bb-minor. A similar shift in notes on the even beats occurs subsequently in m. 9. Meanwhile, the right
hand maintains its two groupings of 6 (1=eighth note) per measure, thus creating a grouping dissonance of G6/4 between the left and right hands. Thus, in Hasty's terms, the second "half note" or fifth eighth note in the left hand of m. 8 leads to a shift in the projected potential of the dotted half note as the beat, but it does not deny the potential for the dotted half note groupings, as an earlier-than-expected event can be followed by an expected one. Indeed, this is certainly the case in mm. 8-9, as the right hand maintains the dotted half note groupings established in m. 7, thereby still realizing the projective potential created in m. 7. Thus, not only has Glass subverted habituation, but he has also conveyed a narrative shift towards unconsciousness that is characteristic of moving from Stage 1 to 2 of the sleep cycle. Importantly, however, there is a mix of both metrical dissonance and consonance, in keeping with the fact we still have several stages to go before reaching REM.

In (c), Glass continues to deploy the variation strategy by using the same four-bar bassline heard in (a) and (b), allowing for processing fluency on behalf of the listener. This time, however, in order to prevent habituation from ensuing, he shifts to triplets in the right hand, creating a G3/2 dissonance that spans the entirety of (c) with no "resolution" until we reach (d). Texturally, the mere fact that there is an extra note above each quarter note creates a much denser texture than what we have heard so far, in keeping with the "accumulative" formal nature of the A section. Thus, this increase in texture and metrical dissonance from (b) to (c) represents an even deeper state of unconsciousness that characterizes the shift from Stages 2 to 3 of the sleep cycle. In terms of metrical entrainment, (c) is significant in the fact that the repetitive triplets cause the listener's expectation of the eighth note as the fastest-moving sound event to be denied, as the "early" second triplet eighth of m. 11 "interrupts" the next expected sound event (i.e., the second eighth note in the left hand of m. 11) to begin to question whether or not the eighth note or the triplet-eighth-note is now functioning as the pulse layer, once again as a means of subverting habituation and keeping the listener engaged.

At the start of (d) in m. 15, Glass once again adheres to the variation strategy by featuring the same harmonic progression we have heard in the previous three subsections, allowing for processing fluency to be achieved on behalf of the listener. This time, however, Glass subverts habituation by greatly thickening the textural density with octave doublings on the downbeat of each measure in the left hand and on almost every eighth note in the right hand of each measure. Additionally, he invokes a similar instance of metrical dissonance as we heard in (b). Thus, between the heightened metrical dissonance and the most extreme textural density we have heard up to this point, Glass effectively indicates we are in Stage 4 of the sleep cycle and on the verge of entering Stage 5 REM sleep. Once again, however, the abrupt shift from G6/4 in (d) yet again creates indirect dissonance from the previous low-level G3/2 dissonance previously heard in (c). Thus, after the listener has become entrained to expect and predict the triplet-eighth-note as the main pulse layer in (c), this expectation is denied in (d), once again causing the listener to be "wrong" in their prediction. Thus, not only is Glass effectively illustrating the dreamer on the cusp of entering REM sleep, he is continuing to subvert habituation and keep the listener engaged, once again optimally employing the variation strategy. Given the fact that this {a, b, c, d} iteration repeats, it is clear that the dreamer wakes up. In Stage 4 of the sleep cycle, preliminary dreams can begin, so it seems that the dreamer began to have memories of their painful past they regret and the emotions intensified so such an extent that they woke up from this nightmare. As we will see in the B section, however, following the second iteration, the dreamer finally confronts and endures the reliving of their painful past.
progression of the left-hand changes in addition to the main pulse layer, creating extreme harmonic and metrical dissonance between the left and right hands. Up to this point, while the meter has been highly unpredictable, the harmonic progression has remained constant, giving the listener at least some sense of predictability. Thus, the introduction of such novel harmonies indicates the first signs of Huron’s rondo strategy. As these novel materials relate to the poetic text, it seems Glass invokes {e}—and, as we will see, {f}—to represent the zenith of the dreamer’s distorted perception of reality that resonates most vividly with Ashbery’s painful declamation, “I keep the spirit of it throbbing still” when reflecting upon his past. In other words, upon the second hearing of the accumulative A section, the dreamer does not wake up but instead confronts and endures his painful past in keeping with Ashbery’s theme of memory.

Example 2.4. Glass, Etude No. 6, mm.13-18

Glass’s Usage of the Rondo Strategy in the B Section

As alluded to earlier, in the B section Glass shifts from the variation strategy to the rondo strategy in which repetition sequences grow gradually shorter and novel material is introduced sparingly. (17) Unlike the variation strategy which hinges on stimulus generalization, the rondo strategy hinges on dishabituation—that is, the introduction of novel materials at crucial points as a means of circumventing habituation, and decreasing the length of future repetition cycles to offset the potentiation of habituation, or the process in which one’s history of habituation can have a facilitative effect on future habituation. In this case, after first introducing the novel materials themselves in {e} and {f}, Glass reuses iterations of the repeated bassline from the A section but only includes three iterations—{d, c, d}—as opposed to the eight heard in the introduction—{a, b, c, d} (repeated)—and this REM sleep B section ends with another iteration of the novel {e} and {f} subsections. Thus, as we will see, Glass’s usage of not only the novel {e, f} subsections but also the shorter and altered ordering of {d, c, d} create a prolonged period of heightened textural density and metrical dissonance that effectively captures the deep REM state of the dream the dreamer is now experiencing. Through analyzing the {e} and {f} sections, we can gain a clearer understanding of how these novel materials function not only to subvert habituation but also to create the “climactic” REM sleep the dreamer is now experiencing and thus create the “one piece, one climax” classical teleology through an unconventional means.

In {e}, a state of extreme agitation is created as we shift from the G6/4 dissonance of {d} to yet another instance of a sub-pulse G3/2 dissonance created by triplets in the right hand imposed over eighth notes in the left hand. This time, however, the underlying harmonic progression of the left-hand changes in addition to the main pulse layer, creating extreme harmonic and metrical dissonance between the left and right hands. Up to this point, while the meter has been highly unpredictable, the harmonic progression has remained constant, giving the listener at least some sense of predictability. Thus, the introduction of such novel harmonies indicates the first signs of Huron’s rondo strategy. As these novel materials relate to the poetic text, it seems Glass invokes {e}—and, as we will see, {f}—to represent the zenith of the dreamer’s distorted perception of reality that resonates most vividly with Ashbery’s painful declamation, “I keep the spirit of it throbbing still” when reflecting upon his past. In other words, upon the second hearing of the accumulative A section, the dreamer does not wake up but instead confronts and endures his painful past in keeping with Ashbery’s theme of memory.

Example 3.1. Glass, Etude No. 6, mm. 34-38

Finally, the last novel subsection Glass introduces is {f}, a continuation of the agitated state from {e} that consists of ascending triplets with slurs grouped into 5s. Once again, the novel bassline not previously heard in the A section upholds the dishabituation principle of the rondo strategy. In addition to the novel harmonies, however, this subsection also introduces a novel metrical grouping dissonance, further highlighting the unique state of REM sleep the dreamer has just entered. Due to the slurs, there is a phenomenal accent implied on the first of each group of five triplets, resulting in a low-level G5/2 dissonance for the first ten pulses and a G3/2 on the last two pulses that functions as a kind of anacrusis to the measure-level projection of each measure in mm. 39-41. This G5/2 in {f} is unquestionably the most extreme instance of metrical dissonance heard in the entire work. In terms of metrical entrainment, the listener has only been exposed to G6/4 and G3/2 dissonances up to this point, so the fact we now have a G5/2 dissonance is sure to engender an even greater sense of unpredictability.
Taking such extreme metrical dissonance along with the fact that the clashing harmonies of E major and F minor in m. 40 are on opposite ends of the circle of fifths indicates the incompatible relationship between objective reality and one's state of extreme unconsciousness during REM sleep. Thus, it seems that the etude is experientially invoking the “throbbing” sensation described in Ashbery's text by creating a sort of harmonic and metrical headache for the listener.

Glass's Usage of the Variation Strategy in the A' Section

In the A' section, we are presented with a “reverse” A section in which the original (a, b, c, d) ordering is reflected into (d, c, b, a), thus creating formal symmetry on the global level of the work as a whole. As in the A section, this section upholds the variation strategy by maximizing processing fluency via a repeated bassline and subverting habituation by varying the levels of textural density and metrical dissonance. Psychologically, it is of importance to note that Glass chose to repeat the A section but not the A' section. As Huron has concluded from numerous empirical studies, listeners strongly prefer early repetition over later repetition in a given work. (19)

As a result of this reversed formal structure, we have the same usage of the variation strategy but in the opposite ordering of what is heard in the A section, creating a decrease in texture and metrical dissonance. Texturally, the notes become less and less varied as we have a gradual return to the simplistic, repeating F4 material from the original (a) subsection. Thus, this creates the inverse of accumulative form: a sort of “decumulative” form in which a groove breaks down into its constituent parts. Metrically, each subsection in this reverse order becomes decreasingly dissonant, which indicates the dreamer is returning to a state of consciousness. As alluded to earlier, as we gradually wake up, our senses become increasingly in touch with reality, and each increasingly metrically consonant subsection in the A' section illustrates this quite clearly. In terms of metric projection, what we heard as a nearly-impossible-to-predict G5/2 dissonance in the (f) subsection has now transitioned to a more limited range of more predictable G3/2 and G6/4 dissonances, and after the last iteration of (c), the listener is finally able to successfully predict the eighth note as the fastest moving pulse layer.

In addition to this “decumulation” in texture and decrease in metrical dissonance, the mere fact that Glass uses the same (d, b, c, a) subsections from the A section clearly illustrates Ashbery’s declamation that “Everything seems like something else...”. In other words, as the dreamer restores their non-distorted sense of reality, there is a growing sense of familiarity with the conscious state they were previously in prior to falling asleep. What is perhaps one of the most brilliant compositional choices Glass makes is how he ends the piece abruptly on a V6/5 chord (a striking departure from literally every other etude in which he resolves the piece with some type of cadence), vividly depicting the sensation of opening one's eyes as they wake up. In other words, the minute the dreamer's eyes open and wakes up, their state of consciousness is fully restored and thus the piece ends. This sudden, unexpected ending of the piece vividly resonates with the final line of text, “I should have waited before I learned this.” In other words, despite the agonizing pain Ashbery experienced in his dream, he still longs for his past, and what he felt as a real experience of his past in his dream has now abruptly ended. Thus, he wishes he had “waited” to wake up from his dream and the reliving of his past before “learning” that his distorted perception of reality (i.e., his past) was only a dream.

Conclusion

In this paper, using Philip Glass's Etude No. 6 as an analytical case study, I have sought to illustrate how classical teleologies can be uniquely constructed by manipulating psychological formal strategies to create narrative in minimalism—a musical style that has historically been referred to by scholars and composers alike as “antiteleological.” While Robert Fink has rightly pointed out that minimalism is indeed teleological but only in a recombinant fashion, this paper has further built on his argument by illustrating how—through the psychological formal strategies

described by Huron—even “one piece, one climax” large-scale classical teleologies can be reconstructed in minimalism through an unconventional means.

Future research is needed to further investigate how classical teleologies function in minimalist works. While this paper has explored the psychological dimensions of classical teleologies in minimalism, additional work on the music-theoretical, historical, and cultural aspects of minimalist classical teleologies is needed in the same way that Fink has examined such dimensions of recombinant teleologies. Furthermore, perhaps future empirical studies might be able to expand upon Huron’s variation and rondo strategies and identify additional means by which repetitive music can be psychologically manipulated in order to minimize habituation and maximize processing fluency. More generally, form in minimalism has historically been neglected, as most scholars dismiss it for its “antiteleological” nature and tend to focus on other aspects of the work at hand. That being said, this paper has sought to illustrate how perhaps there is more than meets the eye when it comes to minimalist form.
Bibliography


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Hunter Hoyle is currently a senior at the University of North Carolina at Chapel Hill, pursuing a Bachelor of Music in Music Education & Piano Performance, as well as a Bachelor of Arts in Psychology. As a performer, he has played with the UNC Chamber Players and Gamelan Ensemble, sung with the Carolina Choir, and served as the accompanist/organist at University Baptist Church. As a teacher, he has taught a variety of piano classes at Durham School of the Arts, and has taught piano lessons through Musical Empowerment, an organization that provides free music lessons to underprivileged children in the Chapel Hill–Carrboro area. As a researcher, his primary areas of interest include the cognition of musical form, the music of marginalized composers from the twentieth century (especially Margaret Bonds and Florence Price), and the practical applications of music-cognitive research to music theory pedagogy and music therapy. Hunter's research endeavors at UNC began through an independent study he took with Professor Aaron Harcus during the Fall 2020 semester. Through that experience, he wrote two papers: one taking a theoretical approach to the analysis of a Schubert sonata, and the other taking a cognitive approach to the analysis of a Glass etude. Hunter later synthesized these two paper topics in his senior honors thesis, where he developed a cognitive theory of formal interference as a means of reexamining Hepokoski and Darcy's sonata theory through the lens of music cognition. Upon graduating from UNC this spring, Hunter will pursue his PhD in Music Theory and Cognition at Northwestern University.