SYNTHESIS & SYNERGY: SCA1, KT, AND HIGHER EDUCATION RESEARCH

SYNTHESIS & SYNERGY: FINDING CONNECTION ACROSS SPINOCEREBELLAR ATAXIA TYPE 1, KNOWLEDGE TRANSLATION, AND HIGHER EDUCATION RESEARCH

By CELESTE SUART, BHSc (Hons.)

A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Doctor of Philosophy

McMaster University DOCTOR OF PHILOSOPHY (2023) Hamilton, Ontario (Biochemistry & Biomedical Sciences)

TITLE: Synthesis & Synergy: Finding Connection Across Spinocerebellar Ataxia Type 1, Knowledge Translation, And Higher Education Research

AUTHOR: Celeste Suart, BHSc (Hons) (McMaster University)

SUPERVISOR: Dr. Ray Truant

NUMBER OF PAGES: xx, 278

Lay Abstract

Graduate students generally receive three types of training at university – how to do research, how to give back to their communities, and how to teach. However, how well a student is trained in each of these tasks is impacted by who teaches them and their learning environment. Not only do students learn skills, but they also pick up on biases and stereotypes connected to their subject area.

This dissertation combines three subject areas. First, biomedical research on the rare, fatal brain disorder Spinocerebellar Ataxia type 1. Second, science communication research on how an ataxia research news website benefits ataxia patients, family members, and even the volunteers to write for the website. Third, education research about how COVID-19 has affected research trainees who work in labs. Doing this many types of research in one dissertation can be challenging, but it trains you how to be a better problem solver.

Abstract

Graduate students are socialized into three key domains of academia throughout their studies – research, service, and teaching. The outcome of this socialization is impacted by a student's disciplinary affiliation, training environment, and supervisory relationship. This multi-disciplinary dissertation represents a scholarly examination of three examples of disciplinary research, service, and teaching. For disciplinary research, we explore characterizing the DNA damage response of ataxin-1, the disease-causing protein of the neurodegenerative triplet-repeat disorder Spinocerebellar Ataxia type 1. For service, we examine the positive impact of a knowledge translation platform for ataxia research ataxia patient and family member readers, as well as its volunteer writers and editors. For teaching, we investigate how the COVID-19 pandemic has impacted graduate students' and postdoctoral fellows' development due to laboratory closures. Further, we return to this examination of the influence of COVID-19 on academia through the exploration of disparities in publication pressure reported by scholars in Canada. Though seemingly disparate research topics, each line of inquiry is grounded within research pragmatism, namely the identification of practical solutions through a clear understanding of a phenomenon. This breadth of research would not be possible without interdisciplinary graduate training, which develops scholars adept at creating innovative solutions to complex or ill-defined problems. Overall, this dissertation offers a snapshot of the opportunities and challenges of interdisciplinary research training within a biomedical research department.

Acknowledgements

There are so many people to thank and not enough page space. I will try to be concise with my gratitude. My pre-emptive apologies for rambling[1].

First, I would like to thank my supervisor Dr. Ray Truant for his unwavering support throughout my undergraduate and graduate studies. You taught me how to be a scientist and conduct research with integrity. Thank you for all your lessons.

I would like to thank the current members of my advisory committee Dr. Lesley MacNeil and Dr. Matthew Miller, for their guidance and support during the last stretch of my graduate studies. Thank you also to my previous advisory committee members Dr. Karun Singh and Dr. Kristin Hope, for their assistance and mentorship at the beginning of my degree.

Thank you to all current and past members of the Truant lab for your commiseration through troubleshooting and revelry in triumphs. A special thank you to Dr. Tam Maiuri, my first project mentor in the lab, for sharing her wisdom and technical expertise with me throughout the years. Thank you to Kaitlyn Neuman for jumping into the deep end with me on a research project in the first year of her MSc. Thank you to former Truant lab undergraduate student Katie Graham, who was my first laboratory mentee. Thank you for helping me learn what it means to be a mentor and joining me as a co-author on two manuscripts. I would also like to thank Jianrun

[1] The first draft of this acknowledgements section was seven pages long. I cut it down four. I am calling that a win.

Xia, Mina Falcone, Claudia Hung, Laura Bowie, Susie Son, Sid Nath, Rebecca Kurtz, Carlos Barba Bazan, Nola Begeja, Natasha Savic, Christina Peng, Sam Laville-Dupuy, and Hassaan Sheikh Muhammad – working in the Truant lab would not have been the same without you all.

Outside of the Truant Lab, I would like to thank Haley Zubyk for all the coffee break conversations and for joining me as a co-author on a STEM education project (especially taking on data collection when I am writing this dissertation). Thank you for your continued friendship and support throughout my graduate studies.

Another special thank you to Dr. Felicia Vulcu, my first research mentor during my undergraduate degree, and Dr. Caitlin Mullarkey, who I began collaborating with as a graduate student. Thank you both for showing me what it means to be a teaching professor. Learning and working with you fundamentally shifted what I wanted to do with my career and research – for which I will be always grateful.

On the topic of teaching and learning, I can not give enough thanks to the MacPherson Institute for Leadership, Innovation, and Excellence in Teaching for the opportunity to be a lead Educational Development Fellow during my time at McMaster University. Being an EDF was a highlight of my graduate studies and let me grow in ways I could not imagine. Thank you to Dr. Elliot Storm, for sharing your wealthy of wisdom on pedagogy and navigating academic systems. You taught me what it means to be a leader in academia, thank you. Thank you to Michelle Ogrodnik and Megan Suttie, I could not have asked for a better lead EDF

team. Your friendship and camaraderie helped me get through some of the most difficult points of grad studies. Also thank you to all other EDFs past and present, especially Lisa Dyce, Brandon Wooldridge, Sarah Whitwell, Samantha Clarke, Jennifer Williams, Creighton Avery, Jee Su Suh, Martha Cassidy-Neumiller, Jess Hider, and William Teal – you made being the EDF program amazing.

I would also like to thank the postdoctoral scholars and educational developers at MacPherson Institute who I worked with over the years. Thank you to Dr. Alise de Bie, whose influence helped me explore accessible education and grow as a disabled scholar. Thank you to Dr. Kelsey Harvey, who has impacted how I approach pedagogical partnerships with students. Thank you to Devon Mordell and Kate Brown (Equity & Inclusion Office) for the work we did together on accessible teaching – it was a joy to write with you.

Also thank you to the other MacPherson Institute staff who I collaborated with over the years, including Kris Knorr, Jennifer Faubert, Erin Allard, Rebecca Taylor, Katrina Espanol Miller, Stephanie Verkoeyen, Julia Evanovitch, Erin Aspenlieder, and Lori Goff. Thank you for showing me the ropes of educational development.

Last, but not least, I would like to deeply thank my family and friends who have supported me throughout my graduate studies. Thank you for indulging my ramblings about science, giving me free food, and encouraging me to keep going forward. Your help and kindness mean the world to me. I am sorry not all of you will be here to see me finally get my PhD, but I know you will be with me in spirit.

To my brother Michael, thank you for reminding me that it is important to take breaks. Your little reminders for me to do self-care with video games and anime were invaluable when I went into workaholic mode. To my parents, John and Theresa, thank you for your support, patience, and love through all my years in school (there has been a lot of them). You have helped me grow into the person I am and believe I can achieve my goals. Dad, thank you for the phone calls while walking home and the car trip sing-a-longs. Mum, thank you for being my favourite second author and the rambles on pedagogical practices. I love you three so much.

Success does not exist in a vacuum. I would not be doing my PhD without the support of all these people. Thank you to everyone who has believed in me and helped me on this journey. I could not have done this without you.

And to you, reader, thank you for taking a look at my thesis. I hope you find what you are looking for. May the journey you are on be overflowed with good things.

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List of Abbreviations

AAO	Age at onset
ANOVA	Analysis of variance
AOA1	Ataxia with ocular apraxia type 1
AOA2	Ataxia with ocular apraxia type 2
ATM	Ataxia-telangiectasia mutated
BSA	Bovine Serum Albumin
CIHR	Canadian Institutes of Health Research
COGFAST	Cognitive Function after Stroke Study
COVID-19	Coronavirus disease of 2019
CV	Curriculum Vitae
DNA	Deoxyribonucleic Acid
HBSS	Hank's balanced salt solution
HD	Huntington's Disease
HiREB	Hamilton Integrated Research Ethics Board
IP Address	Internet Protocol Address
K2A	Knowledge-to-Action
MSc	Master of Science
NCHA II	National College Health Assessment Survey II
NSERC	Natural Sciences and Engineering Research Council
OGG1	8-Oxoguanine glycosylase
ORCID	Open Researcher and Contributor ID

PAR	Poly(ADP-ribose)
PARG	Poly(ADP-ribose) Glycohydrolase
PARylation	PolyADP-ribosylation
PARP	Poly(ADP-ribose) Polymerase
PBS	Phosphate Buffered Saline
PDF	Postdoctoral Fellow
PhD	Doctor of Philosophy
PI	Principal Investigator
Post-COVID	Post onset of COVID-19 pandemic
PPQ	Publication Pressure Questionnaire
Pre-COVID	Pre-onset of COVID-19 pandemic
RPE1	Retinal pigment epithelial cells
RNA	Ribonucleic Acid
SCA	Spinocerebellar ataxia
SCA1	Spinocerebellar ataxia type 1
SCA3	Spinocerebellar ataxia type 3
SCA7	Spinocerebellar ataxia type 7
SoTL	Scholarship of Teaching and Learning
SOP	Standard Operating Procedures
SSHRC	Social Sciences and Humanities Research Council
STEM	Science, Technology, Engineering, and Mathematics
γH2AX	Histone family 2A variant

Declaration of Academic Achievement

Alma Perez, Ismael Al-Ramahi, and Juan Botas performed *Drosophila melanogaster* vial climbing assay experiments in Chapter 2, Figure 5. They designed the experiments, completed the replicates, and wrote a summary of findings which was adapted into the manuscript text.

Tamara Maiuri provided technical support and mentorship for experimental procedures completed in Chapter 2.

Katherine Graham and Theresa Nowlan Suart completed qualitative data analysis as secondary coders in Chapters 3 and 4.

Kaitlyn Neuman supported participant recruitment and completed descriptive statistical analysis in Chapter 5, Table 1.

Ray Truant provided supervision and mentorship through the research and publication process for Chapters 2–5.

Celeste Suart performed the remaining work for this thesis unless otherwise specified. She is the first author of the manuscripts shared in Chapters 2–5, completing 80% or more of all work in each chapter. Celeste is the sole author of content for Chapters 1 and 6, as well as Appendix A. A summary of additional publications and academic contributions made by Celeste during her graduate studies, but outside the scope of this dissertation, can be found in Appendix B.

Chapter 1: Introduction

A doctorate is the highest academic degree awarded in western higher education systems, requiring students to make a substantial contribution to known knowledge by conducting original research (1,2). Doctoral education is highly individualized and varied compared to other higher education degrees, as students play a greater role in shaping the scope of their educational experience to match their research interests (3,4). This training is described as an academic apprenticeship, where the student learns how to conduct research with supervision and support from a more senior scholar (5,6). Through this mentorship by the senior scholar, the PhD student transitions from novice to independent scholar (2,5). These PhD graduates go on to be critical thinkers, innovators, and leaders in diverse areas of society (7,8). Although many doctoral students pursue alternative career paths outside of academia, doctoral programs traditionally prepare the next generation of university faculty members (9–11). This is accomplished through a combination of skills training and socialization.

Graduate Student Socialization

Socialization is the process of acquiring a set of knowledge, skills, values, and norms associated with a particular role in society (11–13). For professional roles, as a person internalizes the expectations and learns the competencies associated with a new role, the person moves from outsider or newcomer status to insider status (11,14). Graduate students, however, experience an unusual double

socialization. As explained by Golde, “new students are simultaneously directly socialized into the role of graduate student and are given preparatory socialization into graduate student life and the future” (15). Put simply, graduate students are socialized into their current role as graduate students, as well as socialized for their anticipated future role, usually assumed to be a faculty member.

Since the inception of the field, student development theory and socialization research have largely focused on undergraduate students (16,17). This mirrors the absence of literature concerning graduate students more generally, which has been attributed to faculty viewing graduate students as colleagues as well as the heterogeneity of graduate student demographics, both of which pose barriers to research (18). However, there has been a push in the past few decades to better understand the development and socialization of graduate students as a means to minimize overall student attrition and increase the proportion od underrepresented minorities obtaining advanced degrees (19–21). Though there are multiple models of socialization, commonalities across models highlight that socialization is a complex, frequently non-linear developmental process involving a person’s past experience, current relationships, and contextual factors (22). The graduate and professional student socialization model by Weidman, Twale, and Stein remain one of the most frequently used frameworks in graduate student socialization research as it reflects the individualistic and diverse nature of graduate education compared to other post-secondary education contexts (22,23).

The Weidman-Twale-Stein framework describes four stages through which graduate students progress as they complete their graduate studies – anticipatory, formal, informal, and personal. These stages are not mutually exclusive but are often overlapping states as a student's identity and commitment to their identity develop over time (23). Anticipatory socialization is when a student starts to be aware of the expectations and procedural responsibilities associated with a role (23,24). Formal socialization occurs through the intentional training of students through structured educational experiences, while informal socialization represents learning done by the student via informal interactions and observations (23,25). Lastly, through the personal stage, a student merges their self-concept and individual values with that of their professional or academic role, working through any potential incongruities to create a new fused identity (14,23). What drives a student’s progression through these stages are core elements of socialization – namely the acquisition of specialized knowledge associated with their academic role, commitment to this role through the investment of financial and social capital, and involving oneself in the activities connected with academia (22,23). Moreover, both the core elements and stages of socialization are impacted by a student's disciplinary affiliation; as program structure, supervision norms, peer culture, and professional expectations vary by discipline (23,26).

Academic Fundamentals: Research, Service, Teaching

Regardless of the disciplinary field, graduate students are socialized into three key facets of academia – research, service, and teaching (Figure 1) (11,24). This is in

part due to the secondary socialization of graduate students as preparation to become faculty members, as research, teaching and service activities largely comprise faculty reward schemes (27–29). Although there are differences in how research, service, and teaching are valued and emphasized across disciplines, this triad of tasks is largely viewed as fundamental components of faculty roles (29).

Conducting disciplinary research has traditionally been perceived as the primary role of university faculty (30,31). This is further reinforced through many tenure and promotion decisions emphasizing research impact and productivity (27,32,33). As such, much of the formal training within graduate programs focus on developing disciplinary knowledge and skills required to undertake research (7,34). In addition to technical competencies, students also acquire more transferable skill sets such as academic writing and presentation skills (35). There are also disciplinary differences in what kinds of research outputs are most well-regarded, with books and monographs emphasized within the social sciences and humanities, while natural and physical scientists tend to value peer-reviewed articles (24,36).

Through interactions with faculty members, peers, and professional organizations, graduate students develop perceptions of what is good research and what makes a good researcher (18). This includes beliefs around productivity, where the adage “publish-or-perish” is used to describe the pressure academics are under to publish high-impact research frequently (37–39). However, publication pressure has also been demonstrated to decrease interdisciplinary and other non-traditional forms of research (40,41). The resulting focus on productivity rather than creativity has been

suggested to limit research innovation (38). Overall, research productivity continues to be explicitly valued and rewarded within academia.

Service work completed by faculty members stems from the historical mission of higher education institutions to support the communities in which they are located and address societal needs (42–44). The term service itself is often nebulous, with other terms such as outreach, advocacy, or engagement also being used (45). Service may include engagement through volunteering with the broader academic community, such as being an officer for a professional organization, coordinating an academic conference, holding administrative roles within departments, or advising student associations (46,47). In contrast, service can also mean public service, such as outreach programs in K-12 schools, partnering with community organizations on philanthropic initiatives, or advocacy work relating to one's research in non-academic spaces (42,48).

There is tension around how service work done in academic and non-academic settings is valued amongst faculty, as service with the academic community is often more valued than local community service with the general public (46,49). There are also disparities among who is doing, and being asked to do, service activities. Faculty members who are women, people of colour, or part of the LGBTQ+ community have disproportionality higher service workloads compared to their peers (49–51). Although their service work is beneficial for the communities they collaborate with, higher service workloads for minoritized faculty members take time away from potential research activities without equal valuation by the

academy (45,50). This bias towards research can negatively impact the tenure prospects of faculty with high service workloads (27,52). Some faculty attempt to blend service and research activities through community-engaged research (Figure 1), where members of the community who will be impacted by the research are involved as equal partners throughout the research process (53). Despite the popularity of community-engaged research with funding and professional organizations, there are mixed perceptions of the value of community-engaged research in tenure and promotion processes (53–55). Faculty have also intermingled service and teaching activities through service-learning (Figure 1), where experiential learning opportunities for students are designed to benefit the communities where academic institutions are located (56). Overall, though service work provides benefits to academic and non-academic communities, there are ongoing conversations on the nature, value, and necessity of faculty service.

Teaching, much like service work, is often minimized compared to faculty member research activities (57,58). Balancing commitments to research, service, and teaching can be overwhelming for faculty, and the pressure to perform well in research for tenure and promotion can lead to less time spent on service and teaching (59). Nevertheless, both research and teaching remain primary components of graduate education and faculty socialization (60–62). Teaching skills, and socialization into the attitudes regarding the value of teaching, are gained through teaching assistantships, sessional teaching appointments, and optional professional development opportunities (62–64). Teaching opportunities

for graduate students not only aid in their socialization and skill development, but are also a source of funding for students (62). Yet graduate student perceptions of teaching mirror that of faculty, that teaching activities remain secondary to disciplinary research (62,64,65).

There are exceptions to this perception. For example, humanities disciplines tend to place further emphasis on teaching, and reward good teachers, compared to natural and life sciences (66–68). The institution a faculty member is associated with can also play a role in their perceptions of teaching, with teaching-intensive universities placing more emphasis on teaching in tenure processes than research-intensive institutions (69,70). Additionally, there has been a rise in teaching-focused faculty appointments across disciplines and institution types, where a faculty member's sole or primary responsibility is undergraduate instruction (71). The creation of teaching-focused appointments demonstrates institutional and departmental commitments to teaching excellence. However, such positions continue the separation of teaching from research activities despite the known benefits of integrating research and teaching activities (72). This has led to faculty creating avenues to integrate teaching activities with research.

The Scholarship of Teaching and Learning (SoTL) is one approach to synergizing research and teaching (Figure 1), where practitioners conduct a context-focused inquiry into teaching and learning within their own disciplinary contexts (73,74). The resulting findings of SoTL research are often more readily applied within classrooms and teaching laboratories due to their foundation in disciplinary

contexts (72). Faculty engagement with SoTL is associated with positive student learning outcomes, as well as value for tenure and promotion (72,75).

Thesis Outline

This work represents a scholarly assessment of each area of my academic socialization – disciplinary research, service, and teaching. Throughout my graduate studies, I was socialized into the academic norms of neurodegenerative disease research, knowledge translation service, and graduate-level laboratory teaching. Each chapter examines my experience in one of these areas through the lens of academic inquiry. The result is an interdisciplinary dissertation with topics ranging from biomedical sciences to education, and research methods spanning quantitative, qualitative, and mixed methods analysis. The remaining pages of this introduction provide a short overview of each area of research touched on within this dissertation to provide context for Chapters 2-5. Chapter 6 will conclude with a discussion on the benefits and challenges of interdisciplinary research.

Research: Spinocerebellar Ataxia Type 1 and DNA Repair

Chapter 2 showcases my disciplinary research on DNA damage and repair within Spinocerebellar Ataxia Type 1 (SCA1). SCA1 is a fatal, autosomal dominant, neurodegenerative disorder characterized by loss of motor control and balance, called ataxia (76). Neurodegeneration occurs predominantly in the Purkinje cells of the cerebellum (77,78). Symptoms first occur in a patient's thirties or forties; however, juvenile forms of SCA1 can occur in adolescence (78). In addition to

ataxia, patients experience difficulty with speech, swallowing, eye weakness, and executive dysfunction (79). The worldwide prevalence of SCA1 is 1/100,000 (80).

SCA1 is one of nine polyglutamine expansion diseases, including Huntington's Disease (HD), spinobulbar muscular atrophy, dentatorubral-pallidoluysian atrophy, and five other spinocerebellar ataxias (81,82). A CAG repeat expansion within the *ATXN1* gene results in an expanded polyglutamine tract in the ataxin-1 protein, which leads to disease (82).

The polyglutamine tract of ataxin-1 is typically encoded by 6 to 42 CAG repeats, with 1-3 histidine-encoding CAT interruptions every 21 repeats (82,83). Disease-associated alleles have 39 or more CAG repeats, with no CAT interruptions (83). Alleles under 39 repeats with no CAT interruptions are mutable, as they do not cause SCA1, but can expand in subsequent generations due to genetic anticipation (80). This suggests that histidine is important for normal ataxin-1 function.

Polyglutamine tract length is inversely correlated with the patient's age at onset of motor symptoms, with the longest tracts leading to juvenile cases (84). Through genetic anticipation, the CAG tract can expand between generations, leading to symptoms occurring earlier in each subsequent generation (85,86). Paternal transmission results in larger CAG tract expansions, with maternal transmission showing less anticipation (86). Non-dividing SCA1 cells also display somatic instability, the expansion of CAG repeats within a patient's cells (87). This highlights the instability and pathological impact of the ataxin-1 polyglutamine tract.

The Ataxin-1 Protein

Ataxin-1 is an 87 kDa protein that is expressed in all tissue types (88,89). The exact function of ataxin-1 is unclear, but it has been implicated in transcriptional regulation and RNA processing (83). Cellular distribution of ataxin-1 is dependent on cell type, where neuronal cells have primarily nuclear localization and non-neuronal cells have primarily cytoplasmic localization (88). Purkinje cells have both nuclear and cytoplasmic ataxin-1 (88). Nuclear localization of expanded ataxin-1 is critical for disease pathogenesis, with the reduction of protein levels or prevention of nuclear entry significantly ameliorating phenotypes in SCA1 models (90–92).

In addition to the polyglutamine tract, there are three key molecular features of ataxin-1: the Ataxin-1/HBP1 (AXH) domain, the nuclear localization sequence (NLS), and serine 776, which can be modified by phosphorylation (Fig. 1). The AXH domain, spanning residues 570–689, is a protein- and RNA-binding motif (93). It allows for homodimerization and binding to various transcription factors through an oligonucleotide/oligosaccharide-binding motif (94–98). The NLS is located towards the carboxyl-terminus, from residues 771–775 (99,100). Modifying the NLS with a K772T substitution disrupts transport to the nucleus and prevents SCA1 pathogenesis in transgenic mice (92). Similarly, preventing phosphorylation at serine 776 with an S776A substitution also impedes pathogenesis in transgenic mice (101,102). The phosphomimetic mutant S776D induces SCA1-like symptoms in wildtype mice (103). There is confusion over how S776 affects pathogenesis,

and debate over what kinase phosphorylates the site (104–106). These three features have been the most well-examined portions of ataxin-1.

DNA Damage Repair and Models of Spinocerebellar Ataxia Type 1

A hallmark of polyglutamine expansion diseases is that a greater number of CAG repeats leads to earlier age at onset (AAO) of symptoms (107). Yet, only 70% of the variance in AAO can be attributed to CAG length in SCA1 (107,108). This suggests other factors may be influencing the progression of SCA1. A single-nucleotide polymorphism (SNP) analysis found that DNA repair genes significantly modify the AAO of SCAs (109). This was a follow-up to the landmark Genetic Modifiers of Huntington's Disease genome-wide association study, which found a significant association between DNA repair proteins and age of motor onset in HD patients (110). DNA repair genes modifying both SCAs and HD progression suggest there may be a common pathogenic mechanism for polyglutamine expansion diseases.

These recent findings have led to the re-examination of past findings which implicated DNA repair in SCA1 pathogenesis. RNA binding motif protein 17, a binding partner of ataxin-1, has been shown to play a role in DNA repair, but the exact mechanism is unclear (111). Overexpression of DNA repair factors replication protein A1 and high mobility group box 1 in SCA1 mouse and *Drosophila* models corrects motor phenotype (112,113). However, the role of ataxin-1 itself in DNA repair has not been studied prior to our research.

Many proteins involved in polyglutamine expansion diseases have now been linked to DNA damage repair, including huntingtin in HD, ataxin-2 in SCA2, ataxin-3 in SCA3, and TATA-box binding protein in SCA17 (114–116). This includes our previous work demonstrating that huntingtin participates in an ATM-dependent DNA repair response (117). Ataxia-telangiectasia mutated (ATM) is an S/T kinase activated by double-stranded DNA breaks, single-stranded DNA breaks, chromatin reorganization, and oxidative stress (118–120). ATM has also been shown to have an irregular expression in SCA1 knock-in mice (113). Together, these points led to our investigation into whether ataxin-1 has a DNA damage repair function outlined in Chapter 2 (121). This work characterized the ATM-dependent response of ataxin-1 to areas of DNA damage, as well as identified serine 186 and 188 in ataxin-1 as phosphorylation sites for ATM (Fig. 1). Overall, this research has laid the groundwork for future exploration of dysregulated DNA repair within SCA1.

Service: Ataxia Knowledge Translation

Chapter 3 features a scholarly assessment of my service work, knowledge translation efforts focusing on ataxia research. The concept of putting research findings into action is not a new one, with the first examinations of how scientific innovations are adopted into everyday practice occurring in the literature in 1903 (122). The terms used to describe such actions have changed considerably over time, including terms such as knowledge translation, knowledge mobilization, knowledge transfer, knowledge uptake, knowledge exchange, science communication, diffusion of innovation, implementation science, or research

utilization (123,124). The variety of terms reflects both disciplinary and geographical differences. For example, practitioners in the United Kingdom or Europe may use implementation science or research utilization to describe the same activities a practitioner in the United States would call diffusion of innovation, or knowledge transfer in Canada (123). Likewise in North American contexts, knowledge translation is used by practitioners from health sciences and natural science backgrounds, while knowledge mobilization is preferred by those in social sciences and humanities (123). Despite efforts by international bodies to create shared language, such as the United Nations University proposing the use of K* in 2012 as a collective shorthand for knowledge sharing terminology, the disciplinary- and geographical-associated terminology has continued to be favoured (125). This has created a siloing effect within the literature, where researchers tend to use the knowledge-sharing terminology they are first introduced to be colleagues, with limited exchanges across terminologies within published literature.

Within this dissertation, we will be using *knowledge translation* to describe knowledge-sharing activities, due to its preference by the Canadian Institutes of Health Research (CIHR) and the World Health Organization (124). The CIHR defines knowledge translation as “the exchange, synthesis and ethically-sound application of knowledge – within a complex system of interactions among researchers and users – to accelerate the capture of the benefits of research” to improve health outcomes (124). In short, knowledge translation focuses on bridging the gap between research and practice, as well as between researchers

and the general public, by making research knowledge accessible for non-specialists to use.

Facilitating the implementation of research findings into practice is the fundamental goal of knowledge translation efforts (126). Simply because a study is published does not mean its findings will be used. Indeed, a review of health sciences literature found only 14% of published findings are ever applied in practice, and this implementation takes an average of 17 years to accomplish (127). Graham and colleagues have named this discrepancy between what evidence exists and what practices we implement the Knowledge-to-Action (K2A) gap (128). There are four common causes of K2A gaps, namely when intended knowledge users do not know information exists, do not understand what information means, do not care about information, or do not agree with the information (129). Each of these causes requires different knowledge translation methods to overcome. Often, however, K2A gaps result from a combination of these four causes. This complexity requires a combination of knowledge translation approaches to begin to bridge the gap.

There are four general categories of knowledge translation approaches; push, pull, linkage & exchange, and intermediary approaches (129). Each category is comprised of multiple strategies, some of which can be used on their own but are often combined to create a layered knowledge translation strategy. Push approaches focus dissemination via researchers ‘pushing out’ knowledge to inform knowledge users, such as through open-access publications or lay summaries (129). Pull approaches focus on knowledge users’ current needs, with researchers

pulling knowledge users into the research process (129). Linkage and exchange approaches try to combine the strengths of push and pull approaches, focusing on partnerships and long-term collaboration between researchers and knowledge users (129). The exchange approach often employed knowledge brokers, who serve to build these partnerships across roles and organizational siloes (130). Lastly, intermediary approaches are used by institutions to coordinate knowledge translation strategies between organizations at the regional, national, or international level (129). Across these four categories of approaches, there can also be different objectives for how researchers hope knowledge users implement research findings; including direct application which changes behaviour, indirect application with changes attitudes or awareness, and tactical applications which change political or structural systems (131). As such, there are a variety of factors to consider when selecting what knowledge translation strategies best match a particular K2A gap.

In addition to which translation strategies to use, one must also consider when to use them. Traditionally end-of-project knowledge translation was the main method for disseminating findings, where all knowledge translation efforts are conducted at the end of a research project (132). The Communications Model by Lavis and colleagues is an example of how to design an end-of-project knowledge translation model to effectively communicate findings to chosen population (133). Integrated knowledge translation, where knowledge translation efforts are incorporated throughout the research process, has become more popular in recent decades

(134). The Knowledge to Action framework is a popular Canadian model of integrated knowledge translation which provided a detailed procedure for how and when to disseminate knowledge throughout research and practice (124,135). Overall, end-of-project knowledge translation tends to be lower cost in the short-term, while Integrated knowledge translation as higher up-front costs and influences longer-term change (129).

My graduate work has largely focused on lay summaries as a means of knowledge translation. This strategy was initially developed as a push approach for end-of-project knowledge translation, but is now being incorporated into a variety of layered knowledge translation approaches (129,133). Lay summaries, also called plain language summaries, are concise, engaging, and clear synopses of a research finding in text format (136). Summaries replace complex jargon and sentence structure with shorter sentences and familiar words, targeting a grade 8 reading level (137,138). This evidence-informed strategy has been used to make research findings from a variety of disciplines more accessible to non-specialist audiences (139–141). Lay summaries overcome common barriers experienced by lay persons trying to access primary research articles, including paywalls, highly technical language, confusing sentence structures, and impersonal writing style (140,141). Despite the clear benefits of lay summaries, researchers often struggle to write in this format without intentional training and practice (138,142,143).

Prior to our research, there was little prior work examining knowledge translation practices targeting ataxia patients and family members. Instead, insights were

derived from general best practices and research on knowledge translation for populations with other neurological disorders such as Huntington's Disease, stroke, or dementia (142,144–146). Although further strides have been made toward better understanding knowledge translation practices within rare disease contexts (147), there has been little follow-up to our work showcased in Chapter 3.

Teaching: Graduate Laboratory Education

Chapters 4 and 5 focus on explorations of graduate education and how trainees were impacted by the COVID-19 pandemic. My research on graduate education is primarily informed through SoTL frameworks, as this inquiry is closely aligned with my disciplinary context as a laboratory-based researcher (74).

Doctoral students from science, technology, engineering, and mathematics (STEM) disciplines in the United States spend six years on averaged pursuing their PhD (148). The limited data examining PhD completion times in Canada suggest similar progression for doctoral students at Canadian institutions (149). Unlike in the humanities and some social sciences, where after coursework is completed graduate students' inquiry is conducted largely independently in isolation, students from STEM disciplines conduct their research in laboratory environments (150).

Academic research laboratories are comprised of researchers from a variety of career stages who are working on related projects which connect to the overall research focus of the principal investigator (PI), who is typically the faculty supervisor for graduate students (151). In addition to the PI and graduate students,

other members of laboratories may include undergraduate students, laboratory technicians, postdoctoral fellows, research scientists, and junior faculty members (152). The composition of lab members depends on disciplinary norms, level of funding, and seniority of PI. This complex ecosystem of researchers within a laboratory environment facilitates graduate students' development as scientists, acquisition of technical skills, and socialization to the norms of their chosen discipline (64,153–155). The laboratory system provides mutual benefit for the PI and graduate students. The PI sponsors students' entry to academia through mentorship, funding, and lab space (156), while students provide PIs with the labour required to generate scientific discoveries (157,158). This mutual exchange of resources and support is the foundation for the cognitive apprenticeship between student and faculty supervisor.

Cognitive apprenticeship theory is an andragogical training model derived from the traditional apprentice–expert model used within the trades (159). This model focuses on learning by doing, often through trial and error with expert feedback from a mentor, where the mentee learns how to approach problems from different intellectual perspectives and critically examine information (159,160). As described by Walker and colleagues regarding graduate student cognitive apprenticeships, the faculty mentor scaffolds the students learning which makes "visible and explicit those aspects of scholarly and professional expertise that are typically taken for granted and thus unarticulated" in addition to tangible skill development (26). There is a significant overlap between cognitive apprenticeship theory and graduate

student socialization, with cognitive apprenticeship focusing more so on the growth of expertise directly relating to a specific role, while socialization focuses on identity development and integration of expertise into a student's sense of self (6,24).

For laboratory-based graduate students, their primary mentor figure is their faculty supervisor. It cannot be understated the importance of the mentor–mentee relationship between supervisor and student, as research has consistently shown that a positive supervisory relationship has the largest impact on graduate student trajectory (151,161–163). However, due to the infrastructure of a research laboratory having several members at different career stages with different socialization experiences, graduate students often have multiple mentors. When first beginning graduate studies, a student may also receive support from postdoctoral fellows, research associates, and senior graduate students within their lab group (152,164). In turn, as the graduate student gains skills and knowledge, they can mentor undergraduate students and more junior graduate students (165,166). This shifting multifaceted mentorship is termed the cascading model by Golde and colleagues, whereby support flows from the more senior members within a laboratory to the more junior members (167). As a graduate student progress through their studies, who they mentor and who they receive mentorship from changes as they gain disciplinary knowledge and confidence.

However, there has been relatively little examination of laboratory-based graduate student development within the literature. As previously stated, most research on student development has focused on the undergraduate level, leaving the

experience of graduate students understudied (16–18). This is a significant gap within the literature, as what research does exist demonstrates poorly supported student development results in higher graduate student attrition, lower publication rates, and worse post-PhD career opportunities (9,168,169). Further, what research that does exist is often multi-disciplinary and misses out on key contextual factors which exist for students who work in laboratory environments (11,22,65). This gap within the literature is what has led me to focus on this area of higher education research. The importance of context within laboratory education research steered me toward using SoTL research frameworks for my inquiry.

Though developed for use within classroom-teaching research, SoTL lends itself to investigations on graduate laboratory education due to its focus on context-focused inquiry and discipline-based lines of questioning (73,74,170). As described by Felten, the five tenets of SoTL research is that it is focused on student learning, grounded within the learning context, methodologically sound, conducted with students partners, and that findings are shared with the research community (74). Though STEM researchers conducting SoTL often report epistemological tension between their quantitative training and the interdisciplinarity of SoTL research, working through these tensions can support professional identity development as researcher-instructors and generate research findings with practical outcomes to improve student learning (170,171). The pragmatism of SoTL, namely its focus on understanding problems and identifying practical solutions, is what lends SoTL to be used in dynamic learning environments such as laboratories.

Figures

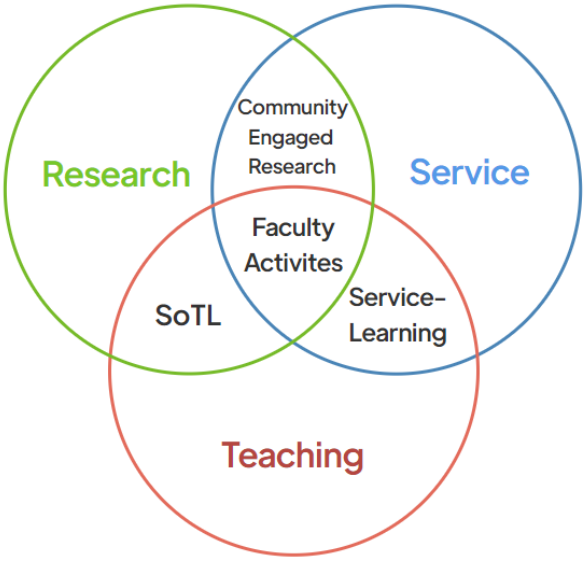

Figure 1.1 Overview of Faculty Activities. Post-secondary faculty members carry out activities relating to research, service, and teaching. Some activities overlap traditional domains, such as community-engaged research (research & service), service-learning (service & teaching), and SoTL (teaching & research).

Figure 1.2 Domain structure of the ataxin-1 protein. Ataxin-1 is an 87 kDa protein with 816 amino acids. It contains a polyglutamine tract (starting at residue 197, orange), AXH domain (residues 570-689, green), and an NLS (residues 771-775, red). Ataxin-1 also has three phosphorylatable serines of interest at positions 186, 188, and 776 (grey). Diagram not to scale. Adapted from Zoghbi & Orr (172).

Chapter 2: Spinocerebellar Ataxia Type 1 protein Ataxin-1 is signaled to DNA damage by ataxia-telangiectasia mutated kinase

The material in this chapter is a reprint of the following publication:

Suart, C. E., Perez, A. M., Al-Ramahi, I., Maiuri, T., Botas, J., & Truant, R. (2021). Spinocerebellar Ataxia Type 1 protein Ataxin-1 is signaled to DNA damage by ataxia-telangiectasia mutated kinase. *Human Molecular Genetics*, *30*(8), 706-715. doi: 10.1093/hmg/ddab074

Changes were made in the following publication for continuity and formatting.

Contributions to Publication

CES was first author of this manuscript and contributed 85% of all efforts relating to this project. CES, TM, and RT designed the project experiments. AMP, IA, and JB conducted the experiment, generated the figure, and wrote the text relating to figure 5. CES conducted the remaining experiments. TM provided technical assistance. CES wrote the manuscript and generated figures 1-4 and supplementary figures. TM and RT edited the manuscript. Funding for this work was obtained by CES and RT.

Implications of Work

Since the discovery of the *ATXN1* gene in 1993, the major hypothesis on the pathogenic mechanism of SCA1 has centred around protein misfolding (173). Inspired by early findings in Alzheimer's Disease and Parkinson's Disease, the basic premise of the toxic aggregate hypothesis for polyglutamine expansion disorders posits that excess glutamine residues result in protein misfolding which leads to protein aggregates, that in turn triggers neuronal dysfunction an neurodegeneration (115,173). The popularity of the toxic aggregate hypothesis dissuaded researchers from exploring other potential mechanisms for decades.

The use of unbiased statistical genetics analysis through a genome-wide association study of 9,000 HD patients and follow-up single-nucleotide polymorphism analysis of 1,000 SCA patients changed the polyglutamine expansion disorder fields (109,110). Instead of findings disease-modifying pathways relating to protein homeostasis and folding, as predicted by the toxic aggregate hypothesis, they found that mutations to genes involved in DNA damage repair, mitochondrial health, and redox pathways influenced disease progression (109,110). This was a surprising finding which sparked a flurry of novel investigations into alternative disease mechanisms for polyglutamine expansion disorders focusing on DNA repair (116).

Although there is strong evidence for DNA repair being implicated in the pathogenesis of SCA1 from genetic studies, the focus of recent SCA1 research has been on ataxin-1 nuclear localization and transcriptional disruptions caused by

polyglutamine expansion through the use of mouse models (90,174). This publication represents some of the first findings connecting DNA repair to SCA1 pathogenesis, which offers a possible explanation of previous genetic analysis data implicating DNA repair proteins influencing SCA1 symptom onset. Using human cell lines, we characterized the novel response of ataxin-1 localizing to areas of DNA damage, how this response is impaired by polyglutamine expansion, and how ataxia telangiectasia mutated (ATM) kinase modules ataxin-1 localization. Moreover, we took a comparative approach highlighting the similarities between the ataxin-1 and the huntingtin responses to DNA damage, which advanced the growing body of evidence for a shared pathogenic mechanism for polyglutamine expansion disorder rooted in DNA repair deficiencies (115,116).

These findings have been shared at international conferences in Canada, the United States, and Italy – sparking discussions with other ataxia research labs to examine markers of DNA damage within their research context. This research also laid the groundwork for further exploration of altered poly(ADP-ribose), a post-translational modification added to sites of DNA damage, within SCA1 fibroblasts (Appendix A). The preliminary findings outlined in Appendix A are not a publishable unit on their own, but my hope is that this line of questioning focused on poly(ADP-ribose) and DNA repair can be continued by future SCA1 and HD researchers.

Since its publication in March 2021, this manuscript has been cited three times.

Spinocerebellar Ataxia Type 1 protein Ataxin-1 is signalled to DNA damage by Ataxia Telangiectasia Mutated kinase

Celeste E. Suart[1], Alma M. Perez[2], Ismael Al-Ramahi[2], Tamara Maiuri[1], Juan Botas[2], and Ray Truant[1]*

[1]Department of Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Ontario, L8N 3Z5, Canada
[2] Department of Molecular and Human Genetics, Department of Molecular and Cellular Biology, Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital, Houston, Texas, 77030, USA

*To whom correspondence should be addressed: HSC4N54, 1200 Main Street West Hamilton, Ontario, Canada L8N3Z5, Telephone: 905-525-9140 x22450, Email: truantr@mcmaster.ca

Abstract

Spinocerebellar Ataxia Type 1 (SCA1) is an autosomal dominant neurodegenerative disorder caused by a polyglutamine expansion in the ataxin-1 protein. Recent genetic correlational studies have implicated DNA damage repair pathways in modifying the age at onset of disease symptoms in SCA1 and Huntington's Disease, another polyglutamine expansion disease. We demonstrate that both endogenous and transfected ataxin-1 localize to sites of DNA damage, which is impaired by polyglutamine expansion. This response is dependent on ataxia telangiectasia mutated (ATM) kinase activity. Further, we characterize an ATM phosphorylation motif within ataxin-1 at serine 188. We show a reduction of the *Drosophila* ATM homolog levels in an ATXN1[82Q] *Drosophila* model through shRNA or genetic cross ameliorates motor symptoms. These findings offer a

possible explanation as to why DNA repair was implicated in SCA1 pathogenesis by past studies. The similarities between the ataxin-1 and the huntingtin responses to DNA damage provide further support for a shared pathogenic mechanism for polyglutamine expansion diseases.

Introduction

Spinocerebellar Ataxia Type 1 (SCA1) is an age-onset neurodegenerative disorder caused by expanded CAG DNA triplet repeats within *ATXN1* (1). ATXN1 is typically encoded with 6-42 CAG repeats, with a CAT interruption every twenty-one repeats (82). Patients with 39-84 uninterrupted repeats will experience SCA1 symptoms; including ataxia, muscle weakness, and difficulty with speaking and swallowing (82). This CAG expansion encodes an expanded polyglutamine tract within the ataxin-1 protein, leading to neurodegeneration within the cerebellum and brainstem (77). SCA1 is a member of the age-onset polyglutamine expansion disease family, which includes Huntington's Disease (HD) (81).

A hallmark of polyglutamine expansion diseases is that a greater number of repeats correlates to an earlier age at onset (AAO) of symptoms (107). This correlation has been well established in SCA1, however, only 70% of the variance in AAO can be attributed to CAG length (107,108). This implies that other genetic or environmental factors affect the progression of SCA1. Single-nucleotide polymorphism (SNP) analysis conducted on a cohort of HD and SCA patients found that variations in DNA repair genes significantly modified AAO for SCA1 patients (109). This was a follow-up to the landmark genetic modifiers of

Huntington's disease genome-wide association study, which also found a significant association between DNA repair pathways and AAO in HD patients (110). The association of DNA repair pathways and the progression of both SCAs and HD suggests there may be a common pathogenic mechanism for polyglutamine expansion diseases.

We have previously characterized the response of the HD protein huntingtin to DNA damage (117). Huntingtin localizes to sites of DNA damage caused by irradiation and oxidative stress (117). This response is dependent on ataxia-telangiectasia mutated (ATM), a serine/threonine kinase activated by oxidative stress, chromatin reorganization, and DNA breaks (118–120). Oxidative stress, induced by reactive oxygen species, has been suggested to play a role in multiple forms of neurodegeneration, including HD, Alzheimer's Disease, and Parkinson's Disease (175–177). The level of oxidative stress has also been associated with disease severity in the related disease SCA7 (178).

The huntingtin response to DNA damage (117) genetic studies indicating HD and SCA1 may share a common pathogenic mechanism involving DNA repair (109,110) led us to hypothesize that ataxin-1 may have a similar response to DNA damage. Using both endogenous and transfected protein models, we show that ataxin-1 localizes to sites of DNA damage. This localization is affected by polyglutamine expansion of the ataxin-1 protein. We demonstrate this response is dependent on ATM kinase activity and characterize an ATM substrate LSQ motif in ataxin-1 at serine 188. Further, we demonstrate in a SCA1 *Drosophila* model

that the reduction of ATM protein levels improves motor phenotype. These results offer a possible biological mechanism for the identification of DNA repair genes as modifiers of SCA1 progression (109) and lay the groundwork for future investigation of ataxin-1 as a potential DNA repair protein.

Results

To determine if endogenous ataxin-1 can localize to sites of DNA damage, immunofluorescence was performed on hTERT-immortalized retinal pigment epithelial (RPE1) cells following irradiation of regions of interest with a 405nm laser (179). Post-irradiation, endogenous ataxin-1 was observed to co-localize with the positive control of huntingtin at the irradiated area (Figure 2.1a).

Next, we asked whether increased polyglutamine tract length beyond the pathogenic threshold of 37-39 repeats would impact ataxin-1 localization to sites of DNA damage. Polyglutamine tract length above 37-39 repeats causes SCA1 (180). To explore the effects of these mutations, we used an eGFP-fused full-length ataxin-1 construct that we have previously characterized (100). Each ataxin-1 construct is identified by the total number of CAG repeats within the construct. Live cell imaging following micro-irradiation was conducted on RPE1 cells expressing each eGFP-ataxin-1 construct (Figure 2.1b). Regions without ataxin-1 puncta were irradiated with a 405nm laser to induce localized DNA damage, then the average pixel intensity of these regions was monitored over time. As ataxin-1 puncta localized into the irradiated region, the average pixel intensity would increase. Similar to endogenous ataxin-1, wild type ataxin-1-eGFP puncta relocated to

regions of DNA damage (Figure 2.1b,c). eGFP-ataxin-1 [Q84], with an expanded polyglutamine tract, had impaired relocation compared to wild type ataxin-1 [Q26] after 40 minutes (Figure 2.1c). Thus, the pathogenic polyglutamine expansion affected the ability of ataxin-1 nuclear puncta to relocate to regions of damaged DNA.

We examined if ataxin-1 was recruited to chromatin following treatment with 100mM potassium bromate ($KBrO_3$), an oxidizing agent which induces DNA base damage (181,182). Protein chromatin retention assays were performed on RPE1 cells transfected with eGFP-ataxin-1 constructs and histone H2B-mCherry transfection efficiency control. Both ataxin-1 constructs displayed recruitment of ataxin-1 to chromatin in response to oxidative stress (Figure 2.1d). Consistent with micro-irradiation experiments, wild type eGFP-ataxin-1 had the highest level of chromatin retention, while polyglutamine expanded eGFP-ataxin-1 displayed impaired retention compared to following oxidative stress (Figure 2.1d). Thus, ataxin-1 chromatin association is induced by multiple types of damaging agents, and polyglutamine expansion impairs this recruitment.

We then investigated if the ataxin-1 response to DNA damage was dependent on ataxia telangiectasia mutated (ATM) kinase activity, similar to huntingtin (117). We performed micro-irradiation assays on RPE1 cells expressing wild type ataxin-1 in the presence of 10μM KU55933, an ATM kinase inhibitor (117,183). The irradiated cells treated with ATM inhibitor exhibited a sharp decrease in overall cell fluorescence, as well as a decrease in the number of fluorescent nuclear puncta

(Figure 2.2a). Efflux of soluble ataxin-1 from the nucleus, followed by degradation was also observed following irradiation. This phenotype has not been previously seen in this model system (Video S1). There was no significant recruitment of ataxin-1 to sites of DNA damage in cells treated with ATM inhibitor (Figure 2.2b). This suggested that ATM may directly phosphorylate ataxin-1.

We used the kinase prediction software GPS 3.0 to determine if ataxin-1 contains an LSQ motif, a consensus substrate recognition motif for ATM (184,185). A putative LSQ motif was identified at serine 188 in ataxin-1. This site is conserved in ataxin-1 across species and shares homology with canonical LSQ motifs (Figure 2.2c). This suggested that ATM could potentially phosphorylate serine 188 in ataxin-1. A conserved serine at position 186 was also identified in our analysis (Figure 2.2c). Predictive analysis with GPS 3.0 did not identify a clear kinase candidate for serine 186. However, we hypothesized it might play a priming role for serine 188, similar to ATM substrate p95 (185). Thus, we considered both serine 186 and 188 modification in our subsequent analyses.

To test whether phosphorylation of serine 186 or 188 affected ataxin-1 localization to DNA damage sites, serine to alanine substitution mutants were generated. RPE1 cells transfected with eGFP-ataxin-1 [Q26] S186A or eGFP-ataxin-1 [Q26] S188A substitutions were subjected to laser DNA damage assays (Figure 2.2d). Despite similar expression levels, there was no recruitment of either alanine mutant to sites of DNA damage. In chromatin retention assays, both S186A and S188A ataxin-1 mutants had impaired recruitment to sites of damage compared to wild

type ataxin-1 following oxidative stress (Figure 2.2e). This suggests that the two predicted ATM substrate residues are involved in regulating ataxin-1 localization to sites of DNA damage.

Based on our results, we generated an affinity purified rabbit polyclonal pS186pS188 ataxin-1 antibody. We then validated the antibody (Figure S1).

We next examined whether modulation of ATM activity affects phosphorylation levels of endogenous ataxin-1 using the pS186pS188 antibody. Upon treatment with $KBrO_3$, there was a significant increase in pS186pS188 ataxin-1 levels (Figure 2.3a), indicating that this kinase substrate site was responsive to oxidative stress. Cells exposed to oxidative stress in the presence of ATM inhibitor exhibited a diminished response (Figure 2.3a). Thus, oxidative stress, which increases ATM activity (186), led to increased pS186pS188 ataxin-1, while inhibition of ATM activity led to decreased pS186pS188 ataxin-1. This is consistent with DNA repair factors signaled by ATM (187).

Our next question was if the reduction of total ATM protein levels was adequate to decrease pS186pS188 ataxin-1 signal. Similar to our kinase inhibition experiments, after 36 hours of siRNA ATM knockdown there was a diminished pS186pS188 ataxin-1 response to oxidative stress compared to control cells (Figure 2.3b). This indicates that both ATM phosphorylation capacity and protein levels impact the presence of pS186pS188 ataxin-1 in response to stress.

Next, we investigated the levels of pS186pS188 ataxin-1 in wild type versus SCA1 human patient-derived fibroblasts immortalized by hTERT, termed TruSCA1. This is a cell model system with the highest potential genetic accuracy to human SCA1 disease with a control line not affected by SCA1 and avoiding transformation that affects TP53 pathways. TruSCA1 line was derived from primary fibroblasts from a 29-year-old affected male with onset of olivopontocerebellar atrophy type I and spinocerebellar ataxia due to a CAG DNA expansion in *ATXN1* of 52 repeats on one allele. Control (TruHD-Q21Q18F) and SCA1 (TruSCA1-Q52Q29M) fibroblasts were treated with HBSS or 100mM $KBrO_3$ for 30 minutes. There was no significant difference in pS186pS188 ataxin-1 immunofluorescent signal with or without the polyglutamine expansion (Figure 2.3c). Similarly, pS186pS188 ataxin-1 levels increased significantly following $KBrO_3$ treatment compared to control for both wild type and SCA1 fibroblasts (Figure 2.3c). This indicates that human endogenous ataxin-1 pS186pS188 levels increase in response to oxidative stress, but this signaling is not affected by polyglutamine expansion.

We wanted to explore if ataxin-1 and ATM directly interacted within cells, and if this interaction was impacted by oxidative stress and phosphorylation capacity of ATM. To examine this, we conducted a co-immunoprecipitation of ATM under conditions of oxidative stress and ATM inhibition (Figure 2.3d). As many DNA damage related protein-protein interactions are transient, we used a 1% paraformaldehyde fixation treatment prior to lysis to stabilize interactions (188,189). Compared to control, there was a decrease in ataxin-1 in anti-ATM immunoprecipitated from cells treated

with 100mM $KBrO_3$ (Figure 2.3d). However, if ATM phosphorylation was inhibited during an oxidative stress event, then more ataxin-1 was present (Figure 2.3d). From this data, we hypothesize that ATM phosphorylation of ataxin-1 is acting like an on/off switch, with ataxin-1 requiring phosphorylation of serines 186 and 188 prior to localizing away from ATM to sites of DNA damage. Further research is required to fully elucidate this mechanism.

Due to our data connecting ataxin-1 to ATM phosphorylation, we then assessed whether SCA1 patient fibroblasts were deficient in DNA damage markers. First, we examined γH2AX (histone family 2A variant), a marker of double stranded breaks, following treatment with bleomycin (190). There was no significant difference in γH2AX levels between wild type and SCA1 fibroblasts in either control or bleomycin treated conditions (Figure 2.4a). Next we examined levels of 8-oxoguanine glycosylase (OGG1), an enzyme in the base excision repair pathway, after oxidative stress (191). Following $KBrO_3$ treatment, SCA1 fibroblasts had an impaired response compared to wild type cells (Figure 2.4b). We then examined levels of pS1981 ATM following oxidative stress treatment, as ATM autophosphorylation at serine 1981 is an indicator of kinase activity and activation *in vivo* (119). Although both wild type and SCA1 fibroblasts had significant increases in pS1981 ATM following oxidative stress treatment, the SCA1 cell response was significantly less than its wild type counterpart (Figure 2.4c). This further implicates dysfunctional ATM phosphorylation in SCA1. These results also suggests that dysfunction with ataxin-1 in SCA1 cells may be involved in the base

excision repair pathway. Further inquiry is required to identify if SCA1 cells have impaired responses with other member of the base excision repair pathway.

To validate our observations *in vivo,* and to assess the effect of reduced ATM function on ATXN1[82Q]-induced nervous system dysfunction, we used a well-characterized *Drosophila* SCA1 model (192). Nervous system-specific expression of ATXN1[82Q] (using the *nrv2-GAL4* driver) leads to progressive motor performance deficits that can be quantified using movement metrics such as speed in a vial climbing assay. *Drosophila* expressing expanded ataxin-1 show increased levels of γH2AV, a marker of double stranded break damage in flies (193) (Figure S3). At 32 days of age, ATXN1[82Q] animals are 5 times slower than healthy controls in climbing assay (Figure 2.5a and b, compare grey lines with blue lines in b). Reduced function of the ATM *Drosophila* homolog, *tefu*, using either an inducible shRNA in the nervous system, or a heterozygous loss of function mutant, robustly ameliorates the ATXN1[82Q]-induced motor deficits (Figure 2.5a and b, compare grey lines with red lines in b). Validation of the inducible shRNA knockdown of *tefu* can be found in Figure S2. These data indicate that partial reduction of *tefu* levels protects from ATXN1[82Q]-induced spinocerebellar ataxia in a *Drosophila* model of SCA1.

Discussion

In this study, we describe the localization of ataxin-1 to sites of DNA damage and that this response is dependent on ATM kinase activity. Additionally, we discovered an ATM substrate site within ataxin-1 and provide evidence that ATM

phosphorylates ataxin-1 at serine 188. Both ATM kinase inhibition and siRNA knockdown result in lower levels of pS186pS188 ataxin-1. We present preliminary evidence that ATM phosphorylation of ataxin-1 modulates ATM-ataxin-1 protein-protein interaction. We also demonstrate that wild type and SCA1 fibroblasts have similar levels of γH2AX, but decreased levels of OGG1 following stress treatment. Finally, we show that reducing levels of the *Drosophila* ATM homolog completely restores motor performance in a SCA1 fly model.

The data suggest that ATM signaling DNA damage repair via ataxin-1 is not affected by the SCA1 polyglutamine expansion. However, we observed a slower dynamic response of mutant ataxin-1 puncta to the regions of DNA suggesting impeded mutant ataxin-1 dynamics may result in poorer DNA damage repair. This is consistent with HD and SCA1 common modifier genes involved in DNA damage repair.

With the identification of the ataxin-1 response to DNA damage, SCA1 joins many other forms of ataxia with pathogenic mechanisms linked to DNA repair (194,195). This includes ataxia with ocular apraxia type 1 (AOA1), AOA2, Spinocerebellar ataxia with axonal neuropathy, and ataxia oculomotor apraxia XRCC1 (176). Dysfunction of ATM itself causes a form of recessive ataxia (196). More recently, the SCA3 protein ataxin-3 has been implicated in transcription coupled repair as well as activating the ATM DNA damage pathway to induce apoptosis (197–200). Preliminary evidence has also suggested that alpha-synuclein can modulate DNA repair in Parkinson's disease (201).

Overall, present findings that heterozygous loss-of-function of ATM homolog *tefu* or knockdown restores motor performance in a SCA1 fly model supports pursuing ATM kinase or protein expression inhibition as a potential therapeutic target for SCA1. Future work is needed to validate whether the best target is enzymatic modulation of ATM kinase, or lowering ATM protein levels, as this DNA repair factor is both an enzyme and a protein scaffold. Further research is also required to identify the priming kinase for serine 186. Additional work is also needed to explore potential deficits in base excision repair in various SCA1 model systems, including flies, mice, and neurons. This will lead to a better understanding of SCA1 pathology and open new avenues to developing potential therapeutics that may impact a broad range of genetic age-onset neurodegenerative diseases.

Materials and Methods

Reagents

All reagents were sourced from Sigma-Aldrich, unless otherwise specified.

Antibodies

The antibodies against phosphorylated serines 13 and 16 of the huntingtin N17 domain were previously characterised and validated (202). Anti-ataxin-1 antibodies(sc-8766) and anti-pS1981 ATM antibody (sc-47738) were from Santa Cruz Biotechnology . Anti-γH2AX antibody was obtained from Abcam (ab2893). Anti-OGG1 antibody was obtained from the Development Studies Hybridoma Bank (AB_10805279). Anti-rabbit IgG conjugated to Alexa Fluor 594 (A-21442), anti-mouse IgG conjugated to Alexa Fluor 488 (A-21200), and anti-goat IgG conjugated

to Alexa Fluor 488 (A-11055) were from ThermoFisher Scientific. For the phospho-specific antibody generation; antibody was raised in New Zealand white rabbits to NH_3-G(p)SL(p)SQTPG-COOH, counter-purified over a non-phosphorylated peptide column then affinity purified over the phospho peptide column through a service by New England Peptides (MA, USA). See supplementary methods for details.

Cells

Human retinal pigmented epithelial cells immortalized with hTERT (RPE1) were from the American Type Culture Collection. RPE1 cells were cultured in DMEM/F-12 1:1 media supplemented with 10% fetal bovine serum and 0.26% $NaHCO_3$ at 37°C in a 5% CO_2 incubator under nitrogen control of oxygen levels to 4%.

TruHD-Q21Q18F wild type cells were generated and cultured as described previously (203). TruSCA1-Q52Q29M hTERT immortalized fibroblasts were generated as follows: SCA1 patient fibroblasts were purchased from the Coriell Institute repository (GM06927). Cells were cultured in MEM with 15% fetal bovine serum and 1X GlutaMAX (Life Technologies #35050). Cells were infected with 1×10^6 TERT Human Lentifect Purified Lentiviral Particles (GeneCopoeia, LPP-Q0450-Lv05-200-S). To aid in infection, 10 µg/ml polybrene was added. After 8 h, cells were infected again and left for 24 h. Media was changed, and cells were left for an additional 48 h. Successfully transduced cells were selected in media with 1 µg/ml puromycin. Cells were grown at 37°C with 5% CO_2 and 4% oxygen.

Transfections

All cells were transfected with TransIT-X2 (Mirus Bio) according to the manufacturer's specifications. All transfections involving ataxin-1 constructs were incubated at 37°C for 8 hours with 1 µg of DNA. Ataxin-1 expression plasmids; eGFP-ataxin-1 [Q26], eGFP-ataxin-1 [Q84]; were generated as described previously(17). EGFP-ataxin-1 [Q26] S186A and eGFP-ataxin-1 [Q26] S188A were generated from eGFP-ataxin-1 [Q26] using Q5 Site-Directed Mutagenesis Kit according to the manufacturer's specifications. All PCR reagents and enzymes were purchased from New England Biolabs. Plasmids were purified via Presto Mini Plasmid Kit (Geneaid) and sequences were verified by PCR sequencing by the McMaster Mobix facility.

Immunofluorescence

Cells were fixed using methanol at -20°C for 20 minutes, then washed with wash buffer (50mM Tris-HCl, pH 7.5, 150mM NaCl, 0.1% Triton X-100). Then, cells were blocked with blocking buffer (wash buffer + 5% FBS) for either 10 minutes at room temperature or overnight at 4°C. Cells were incubated with primary antibodies diluted in blocking buffer for 1 hour at room temperature. Next, cells were washed and then incubated with secondary antibodies diluted in blocking buffer for 20 minutes at room temperature. Following washing with wash buffer, cells were imaged in PBS.

Microscopy

All microscopy was completed using a Nikon A1 confocal system attached to a

Nikon Eclipse Ti inverted microscope, using an PLAN APO 60x/1.40 oil objective or PLAN APO 20×/0.75 dry objective with Spectra X LED lamp (Lumencor) and GaAsP detectors. A 405nm laser which was part of the Nikon A1 confocal system was used for irradiation experiments. 405nm, 489nm, and 561nm lasers experiments were used for imaging.

Micro-irradiation Assay

RPE1 cells were grown in glass-bottom six well tissue culture dishes or eight well µ-slide ibiTreat until 80-85% confluence, then stained with NucBlue (ThermoFisher Scientific) for 15 minutes at 37°C in a 5% CO_2 incubator. Media was aspirated and replaced with Hank's Balanced Salt Solution (HBSS) (ThermoFisher Scientific) immediately preceding irradiation. Using the Nikon A1 confocal setup described in the subsequent section, samples were kept at 37°C with a Tokai Hit Inu Incubation system (model WSKM). A 405nm laser set to 100% power was used to irradiate regions of interest using a scan speed of 1/16 frames per second (512 x 512 pixels). Regions of interest were drawn over areas where ataxin-1 nuclear inclusions were absent. After X-Y coordinates were recorded, cells were either imaged live, or incubated at 37°C for specified incubation times preceding methanol fixations and immunofluorescence. Then X-Y coordinates were revisited for imaging. For live cell imaging, cells transfected with ataxin-1 constructs were irradiated as described above. Cells were imaged at either 1 minute, 2 minute, or 5 minute intervals over a thirty-minute period using confocal microscopy as described in the subsequent section. For ATM kinase inhibition trials, cells were

incubated for 15 minutes in HBSS with 10μM ATM kinase inhibitor KU55933 prior to irradiation.

Average Pixel Intensity Quantification

Average pixel intensity of the regions of interest were measured using ImageJ mean gray function on FITC channel image. Higher intensity indicates presence of ataxin-1 nuclear inclusions. Values were normalized to the average of pre-irradiation control cell values, which had a region of interest defined but were not irradiated. An increase in intensity indicates that fluorescent puncta are localizing into the region of interest. This analysis was conducted at three time points: 0 minutes, 10 minutes, 25 minutes, and 40 minutes.

Chromatin Retention Assay

RPE1 cells were transfected with indicated eGFP-ataxin-1 construct and transfection control histone 2B-mCherry (H2B-mCherry). After 24 hours incubation at 37°C, cells treated with either HBSS (control) or 100mM $KBrO_3$ in HBSS for 30 minutes. Soluble proteins were extracted with cold 0.2% Triton X-100 in PBS for 2 minutes on ice, then cells were fixed with 4% paraformaldehyde for 15 minutes at room temperature. Nuclear intensity was quantified using CellProfiler (204), using H2B mCherry to normalize for variability in transfection efficiency. Intensity was normalized to untreated wild type ataxin-1 conditions.

pS186pS188 Ataxin-1 Oxidative Stress Trials

For trials focusing on ATM phosphorylation capacity, RPE1 cells were incubated at 37°C for 30 minutes with either HBSS (control), 10µM KU55933 in HBSS, 100mM $KBrO_3$ in HBSS, or 10µM KU55933 and 100mM $KBrO_3$ in HBSS. For trials focusing on ATM protein levels, endogenous ATM knockdown was established with 10 µM ATM SMARTpool siGENOME siRNA (Dharmacon, M003201-04-0005) in RPE1 cells. Control cells were treated with 10µM scramble siRNA (Santa Cruz, sc-37007). siRNA was transfected with Lipofectamine RNAiMax (Invitrogen) according to the manufacturer's instructions, then incubated for 36 hours at 37°C. Cells were treated with either HBSS (control) or 100mM $KBrO_3$ in HBSS for 30 minutes. Cells were then fixed with methanol and immunofluorescence was conducted as described above. Raw nuclear intensity was quantified using CellProfiler, with values being normalized to the average of the HBSS control values.

Co-Immunoprecipitation

RPE1 cells were incubated at 37°C for 30 minutes with either HBSS (control), 10µM KU55933 in HBSS, 100mM $KBrO_3$ in HBSS, or 10µM KU55933 and 100mM $KBrO_3$ in HBSS. Cells were trypsinized, resuspended in PBS, then fixed with 1% PFA for 10 minutes. The fixation reaction was quenched with 1M glycine, then lysed in RIPA buffer (50 mM Tris-HCl pH 8.0, 150 mM NaCl, 1% NP-40, 0.25% sodium deoxycholate, 1 mM EDTA, protease and phosphatase inhibitors (Roche)). Input samples were acquired, then remaining lysates were incubated anti-ATM (Novus Biologicals, NB100-104) and protein A sepharose beads overnight with

rotation at 4°C. Beads and proteins were washed three times with RIPA lysis buffer, then denatured with SDS- loading buffer at 100°C for 10 minutes. Samples were then separated by SDS-PAGE and analyzed by western blot with anti-ATM (sc-377293) and anti-ataxin-1 (11750, kind gift from Zoghbi Laboratory (88)) as outlined in supplemental methods.

Drosophila Models and Motor Performance Tests

The *Drosophila* SCA1 model and transgenic lines expressing human ATXN1[82Q] were previously described (192). The inducible shRNA line v108074 specifically targeting *Tefu*, the *Drosophila ATM* orthologue*,* and the control, non-targeting, scramble shRNA v2691 were obtained from the Vienna Drosophila Stock Center. The nervous system driver line *nrv2-GAL4*, and the *Tefu (dATM)* loss-of-function allele *Mi{ET1}tefuMB09945* were obtained from the Bloomington Drosophila Stock Center. For the *Drosophila* motor performance assay, we used an automated data acquisition system. This system taps the vials at 7s intervals and records video files. These files are then processed using a custom-built software that calculates the average speed of the animals in each vial. 10 age-matched virgin females were used per replicate, and at least four replicates per genotype were tested. Animals are transferred into vials containing fresh media daily. For statistical analysis we performed linear mixed models ANOVA between the indicated genotypes using four replicates per genotype. All cultures, breeding and tests were performed at 25^{o}C.

Drosophila Models Genotypes*:*

negative controls: w[1118]/+, nrv2-GAL4/UAS-v2691.

ATXN1[82Q]/scramble: UAS-ATXN1[82Q]F7/w[1118]; nrv2-GAL4/UAS-v2691.

ATXN1[82Q]/dATM-sh1:UAS-ATXN1[82Q]F7/w[1118]; nrv2-GAL4/UAS-v108074.

ATXN1[82Q]/dATM+/-: UAS-ATXN1[82Q]F7/w[1118]; nrv2-GAL4/+; Mi{ET1}tefuMB09945/+

Statistical Analysis

Statistical analysis was completed using GraphPad Prism 8.2.0 for Windows (GraphPad Software, San Diego, CA, USA) and JMP (SAS Institute, Cary, NC, USA). All experiments represent at least three independent biological replicates. Exact parameters including biological replicates and number of cells per biological replicate are reported in the figure legends.

Data normality was determined using D'Agostino-Pearson normality test. Outliers were identified by Grubb's test or ROUT. Significance of non-parametric data was determined by Kruskal–Wallis one-way analysis of variance. Significance of parametric data was assessed by unpaired Student's t-test, one-way ANOVA, two-way ANOVA, linear mixed models ANOVA, or ANOVA followed by Dunnett's post hoc test as appropriate for the dataset. Exact statistical methods used are reported in the figure legends.

Acknowledgments

We thank H. Zoghbi (Baylor College of Medicine) for her kind gift of ataxin-1 11750 antibody. This work is supported by the Krembil Foundation and the Canadian

PhD Thesis – C. Suart; McMaster University – Biochemistry & Biomedical Sciences

Institutes for Health Research (CIHR) Frederick Banting and Charles Best Canada Graduate Scholarships Doctoral Awards (CGS-D), Grant/Award Number: FBD-170797.

Conflict of Interest Statement

None declared.

Figures

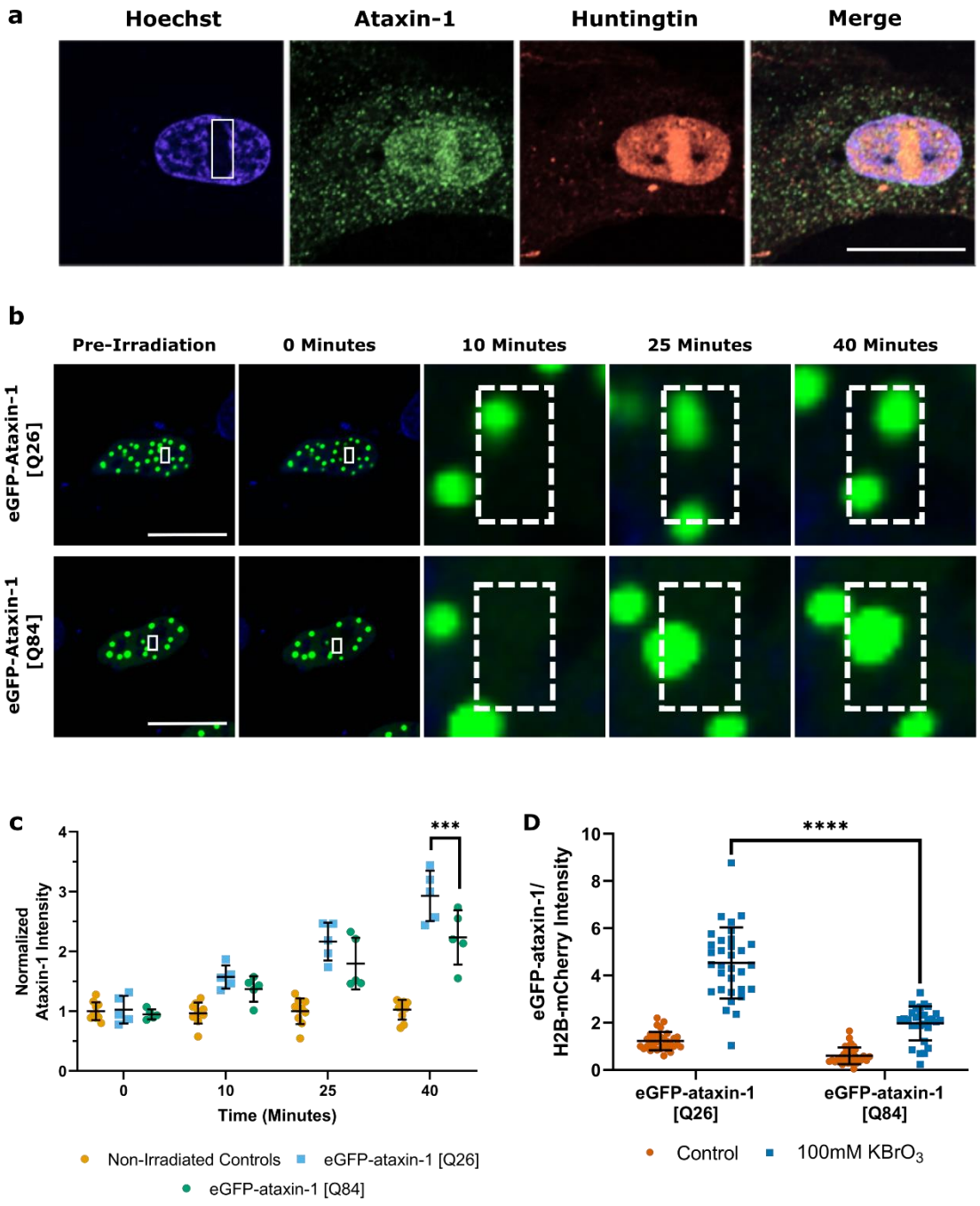

Figure 2.1 Ataxin-1 localizes to sites of DNA damage following irradiation and oxidative stress. All graphs display mean (± SD). Significance values calculated

by two-way ANOVA, *** = $p \leq 0.001$, **** = $p \leq 0.0001$. **a.** Laser micro-irradiation assay of endogenous ataxin-1 from RPE1 cell. White rectangle indicates irradiated area. **b.** Laser micro-irradiation assay of the indicated transfected ataxin-1 constructs in RPE1 cells. White rectangle indicates irradiated area. **c**. Quantification of live cell imaging in part b. Average pixel intensity was calculated for control (0% laser power) and irradiated (100% laser power) regions. Values normalized to the average pre-irradiation control value to account for random movement of ataxin-1 puncta. Both constructs had significant difference from non-irradiated controls starting at 10 minutes. **d.** Chromatin retention assay with indicated transfected ataxin-1 constructs. Nuclear eGFP intensity was quantified after extraction of soluble proteins and fixation. Potassium bromate treated conditions both significantly different from controls ($p \leq 0.0001$). Approximately 30 images were taken per condition with 20-40 cells per image.

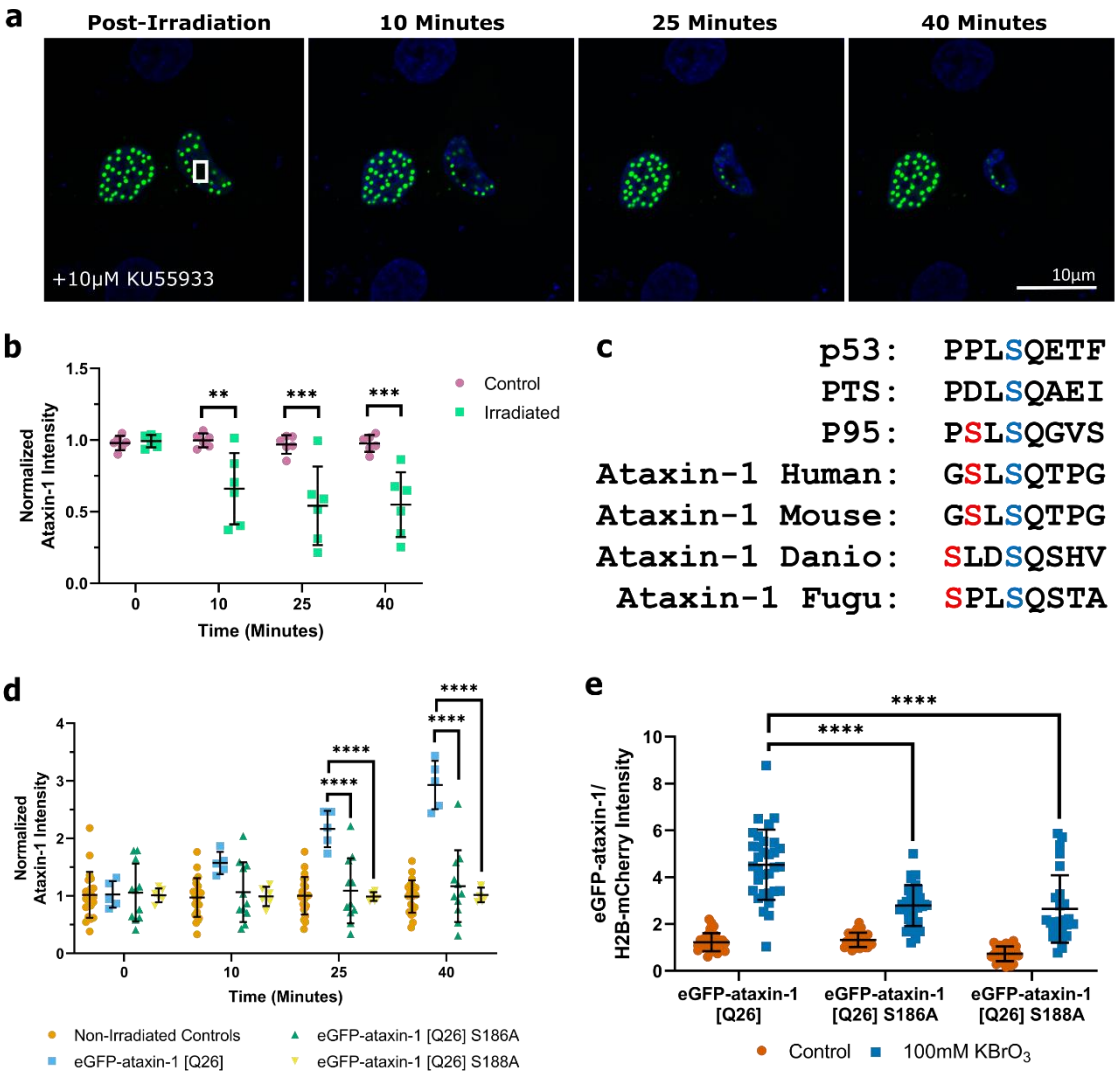

Figure 2.2 ATM inhibition prevents ataxin-1 localization to DNA damage. a. Laser micro-irradiation assay of RPE1 cells transfected with eGFP-ataxin-1[Q26] after incubation with 10μM ATM kinase inhibitor KU55933. **b.** Values from part a were quantified as in Figure 1c. Error bars show mean (± SD) on the basis of six replicates. Significance values calculated by two-way ANOVA, ** = $p \leq 0.01$, *** = $p \leq 0.001$. **c.** Alignment and conservation of predicted ATM kinase site in ataxin-1. p53, PTS, and p95 are canonical ATM substrate provided for comparison.

Residues 185-192 of ataxin-1 shown. Adapted from Kim et al., 1999. Serine 186 shown in red, serine 188 shown in blue. **d**. Quantification of indicated eGFP-ataxin-1 construct recruitment to micro-irradiated regions. Error bars and statistical tests as described in Figure 1c. eGFP-ataxin-1 [Q26] data displayed is replicated from Figure 1c for comparison. **e.** Chromatin retention assay of eGFP-ataxin-1 [Q26] S186A and eGFP-ataxin-1 [Q26] S188A compared to eGFP-ataxin-1 [Q26], using methods and statistical analysis as described in Figure 1d. eGFP-ataxin-1 [Q26] data displayed is replicated from Figure 1d for comparison.

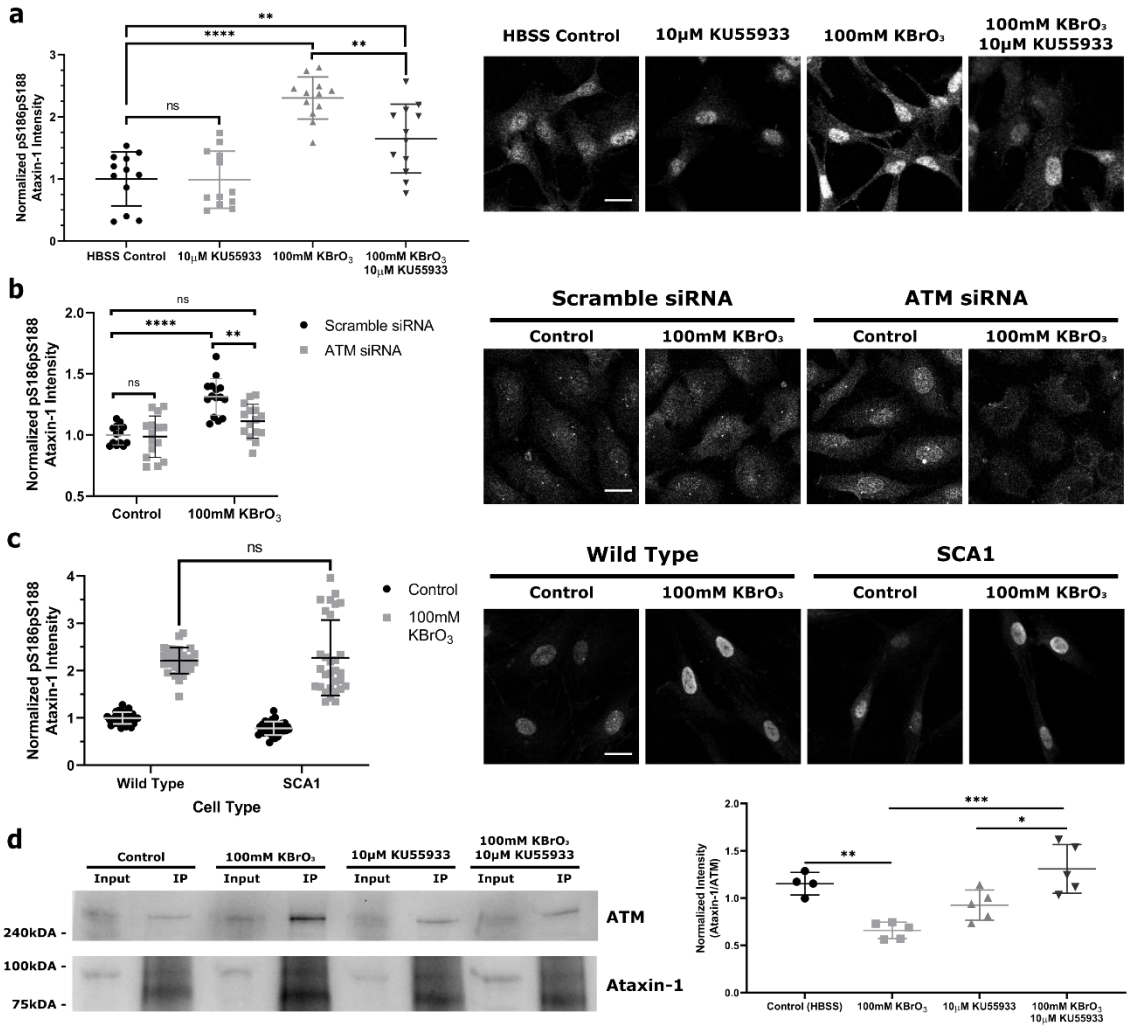

Figure 2.3 Oxidative stress increases pS186pS188 ataxin-1 levels in an ATM-dependent manner. Error bars displays SD. Significance values calculated by one-way or two-way ANOVA, * = p ≤ 0.05,** = p ≤ 0.01, *** = p ≤ 0.001,**** = p ≤ 0.0001. White scale bar indicates 10μm. **a.** Levels of pS186pS188 ataxin-1 during oxidative stress and ATM kinase inhibition. RPE1 cells were treated with either HBSS (control), 10μM KU55933, 100mM $KBrO_3$, or 10μM KU55933 and 100mM $KBrO_3$ for 30 minutes Signal intensity of pS186pS188 staining within the nucleus

was quantified using CellProfiler and normalized to the untreated control condition for each experiment. For each condition, approximately 12 images were taken with 20-40 cells per image. **b.** Levels of pS186pS188 ataxin-1 during oxidative stress and ATM siRNA knockdown. RPE1 cells were incubated with either 10μM scramble or ATM siRNA for 36 hours. Then cells were treated with either HBSS (control) or 100mM $KBrO_3$ for 30 minutes. Quantification completed as described in a, with 15 images taken. There is no significant difference between ATM siRNA knockdown control and treatment groups (P=0.0980). **c.** Levels of pS186pS188 ataxin-1 in wild type and SCA1 patient fibroblasts at basal and DNA damage conditions. SCA1 or wild type fibroblast cells were treated with either HBSS (control) or 100mM $KBrO_3$ for one hour. Quantification completed as described in a, with 30 images taken. Potassium bromate treated conditions are both significantly different from controls ($p \leq 0.0001$). **d.** Ataxin-1 interacts with ATM in response to oxidative stress. RPE1 cells were treated as described in a, then lysed in RIPA buffer. Lysates were incubated with the ATM antibody NB100-104 followed by protein G-sepharose beads. Immunoprecipitates were washed with RIPA buffer and interacting proteins were separated by SDS-PAGE and immunoblotted with the indicated antibodies. Image is representative of four or five independent experiments. One outlier removed by Grubb's test.

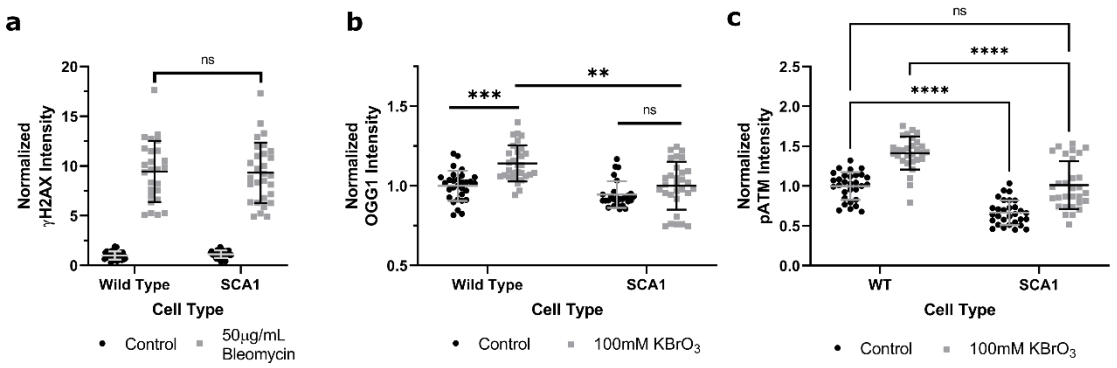

Figure 2.4 SCA1 cells have decreased oxidative stress response, similar double stranded break response to wild type. Quantification was completed with CellProfiler. Approximately 25-30 images were taken per condition with 20-40 cells per image. Significance values calculated by two-way ANOVA or Kruskal–Wallis one-way analysis of variance, ** = $p \leq 0.01$, *** = $p \leq 0.001$, **** = $p \leq 0.0001$. Outliers identified by ROUT. **a.** Wild type and SCA1 fibroblasts were treated with either HBSS (control) or 50μg/mL bleomycin for 1 hour. Nuclear γH2AX signal was quantified. Bleomycin treated conditions are both significantly different from controls ($p \leq 0.0001$). **b.** Wild type and SCA1 fibroblasts were treated with either HBSS (control) or 100mM $KBrO_3$ for 30 min. Nuclear OGG1 signal was quantified. **c.** Wild type and SCA1 fibroblasts were treated with either HBSS (control) or 100mM $KBrO_3$ for 30 min. Nuclear pATM signal was quantified. $KBrO_3$ treated conditions are both significantly different from controls ($p \leq 0.0001$).

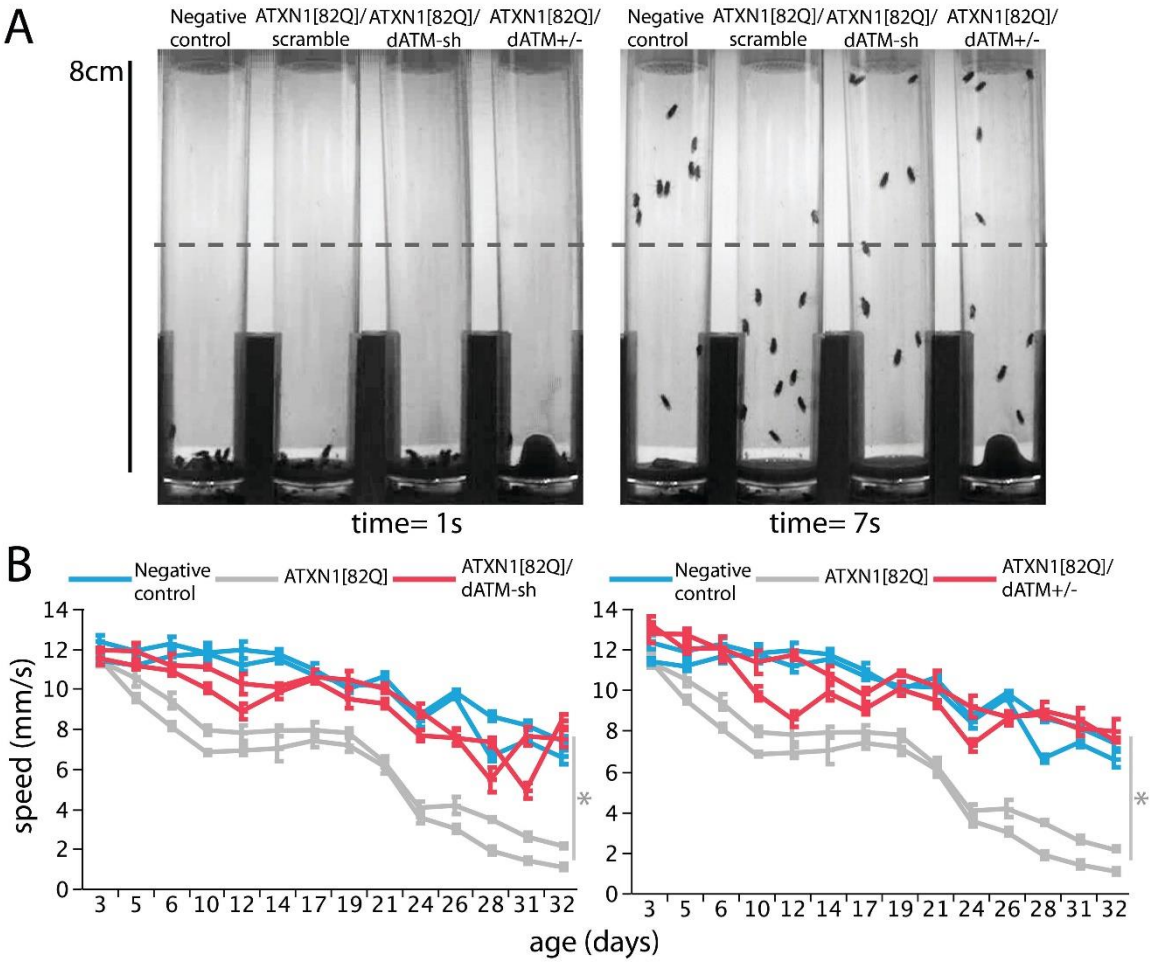

Figure 2.55 Knockdown of the *Drosophila* ATM homolog ameliorates ATXN1[82Q]-induced nervous system dysfunction. **a**, Time-sequence images illustrating the behavior of 24-day-old *Drosophila* females in a motor performance test. At 1s, all 10 age-matched virgin females of identical genotype were tapped to the bottom of a vial. After 7s, most of the negative control (healthy) fruit flies were able to climb past the midway point of the vial, whereas the majority of flies expressing ATXN1[82Q] in the nervous system (nerv-GAL4, also expressing a scramble, non-targeting shRNA) were at the bottom of the vial. ATXN1[82Q]-

expressing animals in which the *ATM* fly homolog was knocked down specifically in the nervous system using an inducible shRNA (ATXN1[82Q]/dATM-sh), or carrying a heterozygous loss-of-function mutation in *dATM* (ATXN1[82Q]/dATM+/-), showed amelioration of ATXN1[82Q]-induced motor impairments. **b**, Graphs representing climbing speed as a function of age in healthy control fruit flies (blue lines), or in flies expressing ATXN1[82Q] alone (gray lines), or together with the dATM-sh or the dATM+/- loss-of-function allele (red lines). Two replicates are shown for each genotype. Error bars indicate S.E.M. The data was analyzed using linear mixed models ANOVA using a total of four independent replicates per genotype. *=$p<0.0001$ between ATXN1[82Q] and either ATXN1[82Q]/dATM-sh or ATXN1[82Q]/dATM+/-.

Supplementary Information

All supplementary information is available online.

Figure S1. pS186pS188 ataxin-1 antibody validation. a. Dot blot assay with ataxin-1 peptide in the unphosphorylated (S186S188), phosphorylated (pS186pS188), and alanine substitution state (A186A188). Protein staining was conducted with 1X Amido Black. **b.** Ataxin-1 knockdown showing pS186pS188 antibody specificity compared to previously validated 11750 antibody. Blots were cut at the 48 kDa marker to probe for ataxin-1 and GAPDH separately. p= 0.0054 for 11750 ataxin-1, p= 0.0354for pS186pS188 ataxin-1. Analyzed by unpaired t-test of three independent replicates. Error bars indicate standard deviation. **c.** Peptide competition assay with unphosphorylated S186S188, phosphorylated pS186pS188, and non-specific TP53 peptide. The cytoplasmic signal is non-specific. Note that in no peptide control, S186S188, and TP53 there is an evenly distributed signal in the nucleus, with transient stress events causing an increase in nuclear signal for some cells. In pS186pS188, the nuclear signal is reduced and no increase in nuclear signal is observed.

Figure S2. qPCR analysis confirms the effect of the *dATM* shRNA and *dATM* loss-of-function allele on *dATM* expression levels. Expression of the inducible *dATM*-shRNA (UAS-v108074) using the panneuronal driver *elav-GAL4[c155]* results in a decrease of *dATM* expression levels of ~ 50%. Expression levels were assessed in whole heads. The real effect of the shRNA on *dATM* expression is probably more robust, since the shRNA is only knocking down the gene in neurons, leaving the glial cells and other tissues in the head with normal dATM expression levels. We also analyzed the expression of *dATM* in heads of the *dATM*+/- animals and again found a decrease of ~50% in *dATM* levels compared to the negative

controls expressing normal *dATM* levels. Error bars indicate standard errors. Statistical significance was established using ANOVA followed by Dunnett's post hoc test. Data represents the average of four replicates per genotype.

Figure S3. Western blot analysis of γH2AV expression in the *Drosophila* CNS. Expression of ATXN1[82Q] in the *Drosophila* CNS for ten days leads to a ~20% increase in the levels of γH2AV as shown in the representative image and adjacent quantification chart. Error bars indicate the s.e.m. p value corresponds to ANOVA followed by Student's t test. Quantification is based on N=6 independent replicates per genotype. p=0.0248.

Video S1. Live Cell Imaging eGFP-ataxin-1 [Q26] with 10μM KU55933. Laser microirradiation assay of RPE1 cells transfected with eGFP-ataxin-1[Q26] after incubation with 10μM ATM kinase inhibitor KU55933 imaged at 1 frame per minute. Increased cytoplasmic ataxin-1 is observed immediately following induction of DNA damage through micro-irradiation.

Chapter 3: Development of a knowledge translation platform for ataxia: Impact on readers and volunteer contributors

The material in this chapter is a reprint of the following publication:

Suart, C. E., Graham, K. J., Suart, T. N., & Truant, R. (2020). Development of a knowledge translation platform for ataxia: Impact on readers and volunteer contributors. *PloS one*, *15*(9), e0238512. doi: 10.1371/journal.pone.0238512

Changes were made in the following publication for continuity and formatting.

Contributions to Publication

CES was first author of this manuscript and contributed 80% of all efforts relating to this project. CES, TNS, and RT conceptualized the study. CS designed the methodology and was the lead author on quantitative and qualitative data curation and analysis. TNS and KJG had supportive roles in the qualitative data curation and analysis process. CES wrote the initial manuscript. KJG, TNS, and RT edited the manuscript. Funding for this work was obtained by RT.

Implications of Work

More people are using the internet to access health research information online than in previous decades (205). However, patients and family members can encounter multiple barriers when trying to access primary scientific research information online, including paywalls and scientific jargon (140). One demonstrated method to make findings accessible and understandable to the general public is the use of plain language lay summaries (140,141).

SCAsource is a website where research information on Spinocerebellar Ataxia and related ataxias is written in plain language by ataxia researchers. Initially launched in September 2018, the idea for SCAsource came from discussions with ataxia patients and the success of HDBuzz, an established knowledge translation website for Huntington's Disease research (145). The goals of SCAsource are two-fold: (i) to make ataxia research more accessible and understandable to patients and families, and (ii) to provide opportunities for ataxia researchers to develop their knowledge translation skills. Altogether, SCAsource aims to improve the overall quality of patient communication in the ataxia community.

This publication is our assessment of the SCAsource platform one year following its launch. We wanted to examine the impact of SCAsource on its readers and volunteer contributors, to ensure we were meeting our knowledge translation goals. Through our mixed-methods analysis, we found SCAsource had positive, mutually beneficial outcomes for volunteers and readers, as well as areas for improvement.

Overall, this publication outlined how other rare disease organizations could launch and evaluate their own knowledge translation websites on limited budgets.

The findings from this paper were used to help SCAsource grow and develop. In 2020, this paper was used as evidence of impact to secure a £2000 bridge funding grant from Ataxia UK to help SCAsource weather the COVID-19 pandemic. This paper also opened negotiations with the National Ataxia Foundation, where in 2022 our organization negotiated a partnership for the National Ataxia Foundation to cover all SCAsource operational costs and pay honoraria for our volunteers – 100 USD for writers and 50 USD for editors and translators per article. These investments by international charities, and encouraging reader feedback, are testaments to the positive international influence of SCAsource.

As of January 1, 2023, SCAsource has published over 220 articles in five languages. We have grown from a team of 10 graduate students and postdoctoral fellows to over 60 volunteer writers, editors, and translators from Canada, the United States, Europe, and South America. This growth would not have been possible without the crucial self-evaluation we conducted as part of this research.

Since its publication in September 2020, this manuscript has been cited four times.

Development of a knowledge translation platform for ataxia: Impact on readers and volunteer contributors

Celeste Suart[1], Katherine Graham[1], Theresa Nowlan Suart[2], and Ray Truant[1]

[1]Department of Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Ontario, Canada

[2]School of Medicine and Faculty of Education, Queen's University, Kingston, Ontario, Canada

To whom correspondence should be addressed: truantr@mcmaster.ca

Abstract

Dissemination of accurate health research information to patients and families has become increasingly important with the rise of the internet as a means of finding health information. However, the public faces several barriers to accessing research information; including paywalls and technical jargon. One method to bridge this gap between patients, families, and research is using lay summaries. SCAsource is an online knowledge translation platform where peer-reviewed research papers on ataxia are translated into lay summaries. This online platform was launched in September 2018, with the goal of making ataxia research more accessible and understandable to patients and families. A secondary goal is to provide opportunities for ataxia researchers to develop and hone their knowledge translation skills, altogether improving the quality of patient communication in the ataxia community.

The aim of this study was to measure the impact of SCAsource on its readers and volunteer contributors after one year of activity. This is to ensure SCAsource is meeting its goals of (1) improving access and understanding of ataxia research to

lay audiences, and (2) improving knowledge translation skills of volunteer contributors.

Two online surveys were launched, one for readers and one for volunteers. Each survey had a combination of multiple-choice, Likert-scale type, and open-ended short-answer questions. Descriptive quantitative analysis was used for respondent characteristics and Likert-type data. A grounded theory coding approach was used to analyze narrative feedback data. We found that SCAsource has mutually beneficial outcomes for both lay person readers and volunteer contributors. Readers have an increased understanding of ataxia research and access to up-to-date information on recent publications. Volunteers develop knowledge translation skills and have increased confidence in communicating results to lay audiences. Areas of improvement were identified to be incorporated into the platform.

We demonstrated that SCAsource improves access to information and understanding of research to lay audiences, while providing opportunities for researchers to develop knowledge translation skills. This framework can potentially be used by other rare disease organizations to launch and evaluate their own knowledge translation websites.

Introduction

Disseminating research knowledge from academia to the general public has become increasingly stressed as an important activity (206,207). Knowledge translation, also referred to as knowledge mobilization or knowledge

dissemination, is the practice of bridging this gap by making knowledge understandable and accessible for users (123,126). The Canadian Institutes of Health Research specifically stress the “synthesis, dissemination, exchange and ethically sound application” as key components of the knowledge translation process (124). One popular knowledge translation model, Knowledge-to-Action, outlines both cycles of knowledge creation and knowledge application cycle involves adapting knowledge to the local context of users, as well as identifying barriers to using and accessing this knowledge (124,135). End users include a variety of individuals, including health care professionals, policy makers, patients, and families (124). As more members of the public use the internet as a means of accessing health information (205), the synthesis and dissemination of research knowledge to lay audiences is becoming a key responsibility of researchers, not merely an occasional by-product.

There are several barriers facing laypersons trying to access research information online. Often laypersons run into paywalls when trying to access primary research (140,208). When they are able to read articles through open access or subscriptions, then issues arise of highly technical language, scientific jargon, and impersonal writing style (140). Although these stylistic choices are appropriate and even encouraged in academia, it can be alienating for lay audiences (139,140).

Lay summaries have been demonstrated to make findings accessible and understandable to these non-specialist audiences (139–141). This style of writing focuses on clear, engaging, and concise writing with the removal of technical

jargon (136). Despite the clear benefit of plain language summaries to lay audiences, many scientists struggle to write effective lay summaries (142,143). This difficulty is caused by many factors, including the vast difference in style between scientific and lay writing, the overabundance of scientific jargon, the heterogeneous nature of the lay audience, and fear of over-generalizing research findings (138).

One platform that has made extensive use of lay summaries is HDBuzz, an online knowledge translation website that focuses on Huntington's disease research (145). Huntington's disease is a fatal neurodegenerative disorder caused by an abnormal expansion of CAG triplet repeats in the huntingtin gene (209). HDBuzz was launched in January 2011 by Drs. Ed Wild and Jeffrey Carroll, motivated by discussions with Huntington's disease patients (145). This platform provides short lay summaries written by clinicians or scientists, explaining how a particular research article fits into the broader Huntington's disease literature (145).

Inspired by HDBuzz and discussions with ataxia patients and family members at the 2018 National Ataxia Foundation's Ataxia Investigators Meeting, we wanted to launch a knowledge translation website focusing on another form of fatal neurodegenerative disease: Spinocerebellar ataxia (SCA). Lack of communication between ataxia researchers and patients has previously been identified as a barrier to patient engagement (210). SCAs are a group of autosomal dominant disorders that primarily cause ataxia, the loss of motor control and balance (211). Six

subtypes of SCA are CAG triplet repeat expansion diseases like Huntington's disease, and there is some similarity in symptoms between these conditions (212).

In September 2018 we launched SCAsource, an online knowledge translation platform where peer-reviewed research papers on ataxia are translated into lay summaries. The main objective of SCAsource is to make ataxia research more accessible and understandable to patients and families. Secondary objectives include providing opportunities for junior ataxia researchers to develop and hone their knowledge translation skills, improving the quality of patient communication across the ataxia community.

This began as a low-budget pilot project, with initial start-up costs (≤500 USD) being covered by members of the SCAsource team. The website was set up through WordPress, an online content management system which allowed for the creation of a professional website by persons with limited web design experience. We chose to create an independent website, as opposed to going through an already existing ataxia organization, in order to limit perceived bias towards a particular geographic location and reach as wide of an audience as possible. Article style and quality assurance guidelines were developed by volunteers who had previous knowledge translation training with other organizations. All content was licensed under a Creative Commons Attribution-ShareAlike 3.0 Unported License, to allow for dissemination on other websites. Initial advertisement of articles was done through social media with support from the National Ataxia Foundation.

Volunteer contributors are recruited through word-of-mouth, primarily at international conferences which focus on ataxia research. We have also had contributors contact SCAsource directly or be referred by current volunteers. They are mainly early career researchers from Canada, the United States, and Europe. The majority of volunteers come from a basic science background. However, more clinical researchers have signed up to write for SCAsource as it has expanded into covering clinical trial results. New volunteers are giving a training guide on how to write effective lay summaries, providing constructive editing feedback, and document guidelines for our two specific article types. These guidelines also provide an overview of minimum quality standards required for publication, timelines for writing articles, and a brief introduction to the knowledge translation literature. These new writers are then paired with more experienced editors during their first few volunteer experiences, to allow for mentorship on knowledge translation to occur through the writing and editing process.

Currently, SCAsource has two regularly-updated article types (Summaries and Snapshots) and two "static" reference resources (a glossary and introduction to Ataxia article). SCAsource Summaries convey the findings and implications of entire research articles, as well as the context in which these discoveries were made. The Summary article type was modeled on the lay article style successfully used by HDBuzz (145). Summaries follow the inverted pyramid structure and best lay summary practices described by Salita (138). SCAsource Snapshots focus on discrete scientific concepts and background knowledge. The Snapshot article type

was launched in April 2019 in response to early reader feedback requesting a deeper explanation of core concepts that appear in multiple SCAsource Summaries. They follow the best practices derived from COGFAST, where members of the public were consulted on what format and content they prefer in lay summaries (142). Topics for Snapshots are generated from search terminology which brings readers to the website or through social media discussions. All SCAsource content is published under a Creative Commons license, making it freely available to distribute.

SCAsource contributors follow a month-long article writing and editing process. At the beginning of each month, a list of research articles for Summaries and topics for Snapshots is circulated amongst contributors. These lists are compiled through a combination of suggestions by email and social media, recently published articles, and search engine information which directs readers to SCAsource. Writers have two weeks to create first drafts, followed by one week of editing by a second contributor, after which they have one week to submit revised articles. Articles can be flagged for a second or third round of editing if further improvements are required. All articles are sent through a copy-editing process to ensure they meet minimum publication standards. This includes a suitability for general audience score of 80% using De-Jargonizer, an automated jargon identification program (213).

In September 2019, we launched an online survey to determine if SCAsource was meeting its mandate objectives of improving readers' knowledge of ataxia

research and volunteers' knowledge translation skill sets. The objective of this study was to determine the impact of SCAsource on its readers and volunteers, establish strengths of the platform, and identify areas of improvement. Through this study, we hope to provide a framework for which other disease groups can launch and evaluate their own low-initial-cost knowledge translation websites.

Methods

Ethics Approval

This study was evaluated by the Hamilton Integrated Research Ethics Board (Project Numbers 7425 & 7426) and determined to be exempted from ethics review due to it being considered secondary use of anonymous quality assurance data.

Study Design, Participants and Recruitment

Two parallel online surveys were launched from September 27, 2019 to December 2, 2019; one for SCAsource volunteer contributors and one for SCAsource readers. Both surveys were administered through the LimeSurvey platform, taking approximately 20-30 minutes to complete. The surveys comprised of Likert-scale and multiple-choice type quantitative questions, along with open-ended qualitative questions.

No financial incentive was given for either survey. To increase the response rate, a follow-up email was sent two weeks after initial contact.

Thirty-three SCAsource volunteers met the selection criteria for the contributor survey. This included (i) having written or edited at least one article for SCAsource

between September 2018-September 2019, and (ii) not being an investigator on this study. Potential respondents were contacted by email through the SCAsource volunteer email list. They were given a letter of information about the study and a link to the online survey.

Our inclusion criteria for the reader survey were individuals who (i) had read at least one SCAsource article between September 2018-September 2019, (ii) were 16 years of age or older, (iii) did not act as a contributor to SCAsource, and (iv) were not an investigator on this study. Estimating the population size eligible for the reader survey was more challenging, as visitor information to the website is measured in IP address statistics. More than one individual could use the same IP address, or one person could use multiple IP addresses. To recruit readers, an email was sent to the SCAsource subscription list (57 eligible participants) including the study letter of information and link to the survey. Two pinned posts advertising the survey were published on the SCAsource website and Twitter account to engage readers who visit the website but are not subscribed for updates.

Analysis

Once data was collected, survey response data was formatted and transferred to the qualitative data analysis software MAXQDA (VERBI GmbH, Berlin, Germany). Descriptive statistics were generated for both volunteer and reader surveys. Website visit data was obtained using the WordPress Jetpack plugin. Quantitative data was entered into GraphPad Prism 8 for analysis and formatting.

To analyze qualitative data, we took a social constructivist approach to grounded theory as described by Charmaz for open coding (214). Two researchers independently completed thematic analysis following a *line-by-line* open coding approach in MAXQDA (214). These initial codes were then synthesized into key categories by identifying interrelated concepts. All codes were reviewed for agreement, with discrepancies resolved through discussion until consensus was reached. This master coding list was given to a third independent researcher to see if the themes previously identified would be subsequently identified by an individual who had not previously worked with the data.

We ensured the rigour of the qualitative analysis by embedding strategies outlined by Lincoln and Guba's four criteria of rigour: credibility, dependability, confirmability, and transferability (215,216). For credibility, we surveyed both contributor and reader populations to ensure a holistic view of SCAsource, along with ensuring investigators had the required knowledge of the website and qualitative coding methodology. For dependability and confirmability, we have included a detailed description of the coding process used with multiple independent coders, which included investigator triangulation to remove potential vias from the analysis. For transferability, we had a clear description of the research context and assumptions.

Results

SCAsource Website Performance

As of January 2020, SCAsource has had over 26,900 views from over 124 countries (Figure 3.1). Website views display seasonal fluctuations, receiving fewer views during winter holidays, with an overall increasing trend between years (Fig 1a). Over half of SCAsource website views originate from the United States, followed by Canada (10%), the United Kingdom (5.8%), China (2.8%), and India (2.2%) (Fig 1b).

Respondent Sample Characteristics

We had an overall response rate of 58% (19/33) for volunteers, which is higher than most e-mail survey response rates (217). Of the volunteers who responded to the survey, 74% (14/19) completed all sections, while 32% (6/19) skipped the qualitative feedback portion. The volunteer demographic information is summarized in Table 3.1. The majority of respondents were either graduate students (32%, 6/19) or postdoctoral researchers (37%, 7/19). Over half of respondents contributed two to three articles to SCAsource between September 2018 to September 2019. A majority of volunteers report they read SCAsource content, with 68% (13/19) visiting the website once a month.

We had 36 respondents to the reader survey, with 75% (27/36) completing all sections of the survey. Although we initially hoped for a greater response rate, this level of participation is not surprising as one symptom people in our target

demographic may experience is difficulty with fine motor tasks. This was highlighted in the quote, “typing is hard” by Reader 18. This barrier inherent to the use of an online survey protocol may explain the reduced rates of response. A more accessible alternative would be to conduct in-person, semi-structured interviews. This approach was not feasible for this study because of the worldwide distribution of SCAsource readers and limited research funding. The demographic information of the reader respondent sample is summarized in Table 3.2.

Over half of reader respondents (53%, n=19) had read over seven SCAsource articles between September 2018 to September 2019. This high level of engagement may be explained by our recruitment using the SCAsource subscription email list, as 39% (14/36) of respondents reporting using the subscription list. Readers reported frequently searching for ataxia information, with 82% (29/36) searching online once a month or more. The sources that readers reported using most frequently were the National Ataxia Foundation (64%, n=23), an American ataxia charity located in Minnesota, and search engine results (61%, n=61). The SCAsource website was the third most used source of ataxia information at 56% (n=20). When asked where they find out about SCAsource content, the top sources cited by readers were the SCAsource website (39%, n=14), SCAsource subscription list (39%, n=14), the National Ataxia Foundation’s social media (36%, n=13), and search engine results (28%, n=10).

Impact of contributing to SCAsource on volunteers

Feedback from volunteers on the impact of SCAsource on their skill development was generally positive, as depicted in Figure 3.2. Over half the volunteers (58%, n=11) agreed that contributing to SCAsource improved their writing or editing skills, with 90% (n=32) saying it improved their confidence when communicating to lay audiences (Figure 3.2). Volunteers also reported the amount of time they dedicate to knowledge translation activities increased (74% agree or strongly agree, n=14), although the majority rated it had no impact on their time management skills (63% neutral, n=12) (Figure 3.2). Sixty-two percent (12/19) agreed that volunteering for SCAsource was beneficial to their development as a scientist, with 53% (10/19) stating the experience enhanced their understanding of ataxia literature (Figure 3.2). The majority of respondents (89%, n=17) agreed they saw volunteering for SCAsource as a way to give back to the ataxia patient community (Figure 3.2). Based on these quantitative measures, SCAsource volunteers reported a gain in knowledge translation skills, including writing, editing, and lay audience communication, on top of increased time spent on knowledge translation activities.

Similar themes of skill development and confidence in knowledge translation also emerged from the analysis of qualitative responses. Table 3.3 outlines the key themes identified from volunteer narrative data with representative quotations.

Volunteers reported that their experience with SCAsource changed their writing style when communicating with a lay audience. This includes how they structure information, their use of understandable terminology, and identifying key takeaway

messages from research articles (Table 3.3). For some, contributing to SCAsource made them intentionally self-reflect during the lay summary writing process. As one volunteer explained, contributing to SCAsource “forced me to slow down and consciously question my word selections,” (Volunteer 1, Principal Investigator). As it has been previously shown that researchers struggle with choosing appropriate lay terminology (143), that our volunteers are reporting this level of conscious awareness of word choice is promising.

Multiple volunteers also identified improved confidence in knowledge translation as the main impact SCAsource has had on them, mirroring the quantitative Likert-style data (Figure 3.2). This is likely tied to the high proportion of volunteers for whom SCAsource was one of their first opportunities to engage in knowledge translation. As described by Volunteer 12 , “I'm not used to communicating others’ results to lay audiences and this has allowed me to practice”. This “opportunity for practice” (Volunteer 9, Graduate Student) was highlighted as a main strength of the SCAsource initiative overall.

The other key strength of SCAsource from the perspective of volunteers was the potential utility to patients and families. Volunteers specifically liked the breadth of topics covered and the emphasis of current research being quickly communicated (Table 3.3).

When asked about potential areas of improvement, contributors identified training for new volunteers and public awareness of SCAsource. Currently, when new

volunteers are onboarded, they are given three documents outlining the SCAsource guidelines on summary writing, Snapshot writing, and editing. In total there are six pages of readings, with additional suggested readings for those interested. Volunteers suggested this training could be more engaging, such as a video or web module (Table 3.3). Volunteers also pinpointed visibility and general awareness as an area of improvement (Table 3.3). This is consistent with informal feedback received when new contributors contact the SCAsource executive. Increased social media use was suggested as a potential solution.

Volunteers also expressed that the general concept of SCAsource was a good idea and gave encouragement for the initiative to continue (Table 3.3). Some volunteers also expressed being “grateful for the opportunity to contribute” (Volunteer 7, PDF) to SCAsource. This reflects the overall positive impression that contributors have of SCAsource, both with regards to personal skills development, increased confidence, and being able to make an impact on the SCA community.

Impact of SCAsource content on readers

Readers reported an overall positive effect of reading SCAsource content (Fig 3). Over 88% (n=32) agreed that reading SCAsource increased their understanding of ataxia research, while 83% (n=30) reported they have learned more about ataxia (Figure 3.3). When asked if SCAsource helped them feel more connected to ongoing ataxia research, 86% (n=31) of respondents agreed (Figure 3.3). A majority (94%, n=34) reported trusting SCAsource as an unbiased source of information (Figure 3.3). Responses were more varied when polled about how

SCAsource influenced their interest in participating in current ataxia research or clinical trials. Sixty-one percent (22/36) agreed that reading SCAsource had increased their interest in participating in such studies, while 39% (n=14) were neutral on the subject (Figure 3.3).

Readers were then asked to rate how helpful they found four different types of content on SCAsource; Summaries, Snapshots, the glossary, and the “What is Ataxia?” information page (Figure 3.4). Summary and Snapshot articles represent the majority of SCAsource content. Summaries are longer texts (800-1000 words) where scientific research is summarized and reported on. SCAsource snapshots are 400 words or less, focus on explaining one scientific topic clearly and concisely. The glossary and “What is Ataxia?” information page are static pages on the SCAsource platform that are infrequently updated. The glossary contains commonly used words across all article types. The “What is Ataxia?” page is aimed at readers who are new to ataxia and is written as a general overview of ataxia information covered on the website.

Both SCAsource Summaries and Snapshots were the content types rated most helpful by readers (Figure 3.4). A third of respondents (11/33) classified Summaries as extremely helpful, while 42% (14/33) ranked Summaries as very helpful (Figure 3.4). Newer readers rated Snapshots as extremely helpful (23%, 8/33) compared to summaries (Figure 3.4). However, over half of readers (55%, 18/33) reported Snapshots as very helpful (Figure 3.4). Both static pages had lower helpfulness from readers. The glossary ranked extremely or very helpful by 57%

(19/33) of readers, with 43% (14/33) classifying it as moderately or slightly helpful (Figure 3.4). The “What is ataxia?” page had more variability in responses. Although 60% (20/33) described this content as extremely or very helpful, the remaining 40% (13/33) of readers described it as moderately, slightly, or not at all helpful. Overall, readers viewed frequently updated content, such as Summaries and Snapshots, as more helpful to them compared to static content on SCAsource.

Through analysis of narrative data, we took a closer look at what exactly readers found helpful about SCAsource content. Themes that emerged included an emphasis on clarity and access to information, as well as suggestions to improve the SCAsource initiative. Key themes from SCAsource readers, along with representative quotations, are outlined in Table 3.4.

The majority of reader respondents appreciated the easy-to-understand content, that SCAsource is an accessible resource, and that SCAsourse provides information about ongoing research (Table 3.4). As Reader 7 explained, “The articles are easier to understand than most ataxia articles”. A few also mentioned they like how SCAsource provided links to the original research, as well as additional resources, so that they could explore topics further. This mirrors past findings highlighting patient interest in primary scientific literature (140). There was also an emphasis on “up to date” (Reader 25) research and being able to see progress being made. Readers’ motivation for their interest in SCAsource differed – from understanding their own condition, a child’s, or a friend’s.

A variety of improvements for SCAsource were suggested, with the theme of current and ongoing research again emerging (Table 3.4). Readers requested more information on research they could participate in, what research questions are being investigated, where research is taking place, and who are the scientists doing this work. A handful of readers requested more frequent updates to the website, again tying into this idea of receiving the latest updates. Like SCAsource volunteers, readers also identified advertising and communication as an area of improvement. In addition to the common themes for suggested improvement, some suggestions stemmed from individuals' personal preferences or needs, including a request for translation to a particular language and a request for promotion on a specific social media platform. While these will be considered in future plans for SCAsource, they will be lower priority items.

We were surprised by the number of reader respondents who advised that there were no areas of improvement for SCAsource (Table 3.4). When asked about how SCAsource could be improved, one reader answered "I don't know. Everything seems correct." (Reader 4). This supports that the SCAsource platform is currently working. Similar to how volunteers were grateful for participating in SCAsource, many readers also gave thanks for the creation of SCAsource. Readers expressed that it was an "excellent resource" (Reader 29) and asked that volunteers "Keep up the good work" (Reader 10).

Discussions

In this study, we assessed the self-reported impact SCAsource has on its readers and volunteers. This was done through a mixed-methods analysis of online survey data from 36 readers and 19 volunteers. Overall, both groups reported a positive evaluation of SCAsource. We demonstrated that the dissemination strategy used by HDBuzz (145) can be modified successfully to serve other disease interest groups.

Over the past 17 months, SCAsource has on the whole observed an increasing trend of views (Figure 3.1a). Views display some seasonal trends, with lower views over the winter holidays, a pattern known to occur with platforms not selling commercial goods. SCAsource also had spikes in view count in both October 2018 and 2019 (Figure 3.1a). We postulate that could be in part due to increased sharing of SCAsource content following International Ataxia Awareness Day on September 25. Over 70% of SCAsource views originate from primarily English-speaking nations, with 64.7% coming from Canada and the United States (Figure 3.1b). This is reflective of the location of SCAsource contributors, who are primarily from laboratories located in North America. If SCAsource is to expand its readership to reach more ataxia patients and families, it will also need to expand its volunteer base to include more researchers from international laboratories. Volunteers with fluency in languages other than English will help expand SCAsource from a unilingual to a multilingual initiative, following a similar trajectory to HDBuzz (145).

Current volunteers reported a key strength of SCAsource was the opportunity to practice knowledge translation. This opportunity for practice and training is possibly what led to the self-reported gains in knowledge translation skills, as well as improved confidence in communicating with lay audiences. This suggests that SCAsource filled a gap in training for researchers, giving them a supportive environment with constructive feedback to improve their lay summary writing. This is further reflected by the request for more extensive knowledge translation training for volunteers.

In addition to an increased understanding of ataxia research, SCAsource readers reported they felt an increased connection to ongoing ataxia research through this platform. The theme of up to date, current research was present throughout multiple sections of the reader survey responses. Readers had a preference for SCAsource content which updated every week over static informational content. Access to information about ongoing ataxia research was cited as both a strength and a potential area of improvement. This indicates SCAsource is on the right track with regards to summarizing recently-published research, but we could expand this area more. In response to this feedback, SCAsource is planning to launch a new article type that will give information about ataxia research laboratories. This will include where the laboratories are located and what areas of research they are pursuing. Our aim is that this new article type will meet the need of readers wanting to learn more about ataxia researchers, the research process, and ongoing studies.

Readers had more mixed responses with regards to whether reading SCAsource content increased their interest in participating in clinical trials (Figure 3.3). Past research on barriers to patient participation in clinical trials have identified lack of information and understanding as a barrier (218,219). Conversely, investigation into neurological clinical research participation has found that receiving information from a trusted source is a key motivator for patient participation (220). SCAsource does not actively advertise clinical trial recruitment. Its focus is on explaining results from published clinical trial data, as well as clarifying methodological procedures common across trials. Despite this, over 60 percent of reader respondents indicated their interest in clinical trial participation has increased (Figure 3.3). However, it can be argued that patients who are already more interested in research participation could be more likely to seek out research information. For this reason we must be cautious not to draw direct causation from these results. Further analysis with a larger respondent sample would be needed for future investigation into this topic.

Suggested areas of improvement from both volunteers and readers point to growth opportunities for SCAsource. This includes more frequent article updates and additional training for volunteers. This feedback points to a well-received knowledge translation website that has room to grow, if additional financial support can be found.

Themes from both surveys also demonstrate that this kind of knowledge translation platform can serve both the research community and the community of those

affected by ataxia (patients, families, friends). Embedded in the feedback from both surveys is the respect and gratitude each community has for the other. There was no sense of imbalance, incorrect focus, or one community benefiting over the other. Early career researchers were able to practice valuable knowledge translation skills, while readers gain knowledge about ongoing ataxia research. This positions SCAsource as a mutually beneficial platform connecting research and lay ataxia communities.

We propose that knowledge translation set-ups similar to HDBuzz and SCAsource could be used by other disease organizations, especially those concerned with rare diseases. More common research areas, such as cancer, heart disease, and diabetes, tend to have more established knowledge translation initiatives (221–223). Conversely, rare disease organizations have identified knowledge translation as a needed area of growth (224). One potential barrier is cost, as rare diseases typically receive less research funding and overall investment due to impacting only a small portion of the population (225,226). The knowledge translation set-up we outline in this manuscript reduces barriers to entry due to its low cost. This would allow for organizations to begin a knowledge translation initiative and generate enough interest to attract external funding to continue & improve efforts over time.

Multiple knowledge translation models have been documented in the literature, with overlap allowing for key themes to emerge from the discipline (227). Such themes include the importance of knowledge translation being ongoing interactive processes with stakeholders, and involving multiple people with varying

perspectives about ongoing research (228,229). The Knowledge-to-Action model, emphasizes the recurrent nature of knowledge creation and implementation action cycles (124). However, these existing models do not address specific issues that are relevant to the rare disease context (227).

Across knowledge translation models there is an emphasis on monitoring outcomes, including improved survival and quality of life (227). However, the novel treatments for rare diseases, including ataxia, tend to have incremental effects over the span of years (227). Another assumption by knowledge translation models is that the knowledge being translated has immediate clinical impact for the reader and their healthcare decisions. However, most research that SCAsource is asked to cover are in either pre-clinical or in early clinical trials. These discoveries do not have an immediate effect on the reader's care. Rather than traditional outcomes measured, learning more about these findings may influence a reader’s choice to participate in research, or provide hope that new discoveries are being made.

Study Limitations

A limitation of this study was the use of a self-reported online survey format for gathering data. As previously discussed, the use of this method may have been a barrier to readers experiencing difficulty with typing and other fine motor tasks. A more accessible alternative for future work would be conducting verbal, semi-structured interviews, either in-person or online through video conferencing. We believe this is one likely reason the number of respondents to the reader survey was lower than we wanted. Using number of unique IP addresses visiting the

SCAsource website between September 2018 and January 2020 (approximately 11,331) to estimate total readership, the respondent sample represents less than 1% of total SCAsource readership. For this reason we may not have reached saturation of themes from narrative data from readers. Our population sample may also have been biased towards more frequent readers of SCAsource. This is supported by over half of reader respondents reporting reading 7 or more SCAsource articles (Table 3.2). Thus, the views expressed by the majority of reader respondents may not hold true for more casual readers of the website.

A second limitation is that our Likert-type scales focused on self-reported outcomes which were not objectively assessed through other means. Future work should include assessment of whether volunteer and reader self-reported gains align with gains measured through other objective means.

Conclusions

We found that SCAsource has mutually beneficial outcomes for both lay person readers and volunteer contributors. Volunteers develop knowledge translation skills and have increased confidence in communicating results to lay audiences. Readers have an increased understanding of ataxia research and access to up to date information on recent publications. Areas of improvement were identified and will be worked towards to improve the SCAsource initiative. We build on past work by HDbuzz (145) to demonstrate this knowledge translation framework is effective in the context of other rare diseases. Further, we provide a foundation on which others can evaluate the effectiveness of their own knowledge translation websites.

Acknowledgments

The authors would like to thank all individuals who responded to the volunteer and reader surveys. Many thanks as well to all current SCAsource volunteer writers and editors whose efforts made this website a reality. This work would not be possible without the support of both the ataxia researcher and patient communities.

Copies of SCAsource training materials and resources are available upon request by email (truantr@mcmaster.ca).

Supplementary Information

All supplementary information is available online.

S1 File. Online Survey Protocol.

Tables

Table 3. 1 Volunteer respondent characteristics.

Characteristic	**N (%)**
Position	
Graduate Student	6 (32)
Postdoctoral Researcher or Fellow (PDF)	7 (37)
Principal Investigator	2 (10)
Other*	4 (20)
Articles Contributed to SCAsource	
1	3 (16)
2 to 3	11 (58)
4 to 5	2 (10)
6 or more	3 (16)
Readership of SCAsource	
Yes	16 (84)
Yes, but only articles to which they contributed	3 (16)
No	0 (0)
Frequency of Reading SCAsource	
Once every few months	4 (21)
Once of month	13 (68)
Once a week	2 (10)

*Examples of “Other” category positions included research technician, consulting scientist, and medical writer.

Table 3.2 Reader respondent characteristics.

Characteristic	N (%)
SCAsource Articles Read	
1 to 2	4 (11)
3 to 4	4 (11)
5 to 6	9 (25)
7 or more	19 (53)
Frequency of Searching for Ataxia Information	
Less than once a year	1 (3)
Once every few months	6 (17)
Once a month	11 (31)
Once a week	11 (31)
More than once a week	7 (20)
Source of Ataxia Information	
SCAsource Website	20 (56)
Search Engine (Google, Bing, Etc.)	22 (61)
National Ataxia Foundation	23 (64)
Social Media (Facebook, Twitter, Instagram)	5 (14)
Shared Friends & Family	1 (3)
Other**	5 (14)
Source of SCAsource Article	
SCAsource Website (Direct Visit)	14 (39)
SCAsource Subscription Email List	14 (39)

Search Engine Result	10 (28)
National Ataxia Foundation (Social Media)	13 (36)
Social Media (Facebook or Twitter)	4 (11)
Shared Friends & Family	2 (6)

**Examples of “Other” category sources of ataxia information European ataxia organizations, social media, and health news platforms.

Table 3.3 Volunteer themes and representative quotations.

Knowledge Translation Skill Development	
Improved communication of scientific findings to lay audiences through knowledge translation techniques	“It is very important that scientists explain lab findings to the general public and (even more important) the SCA patients. Volunteering helps to explain difficult scientific terms to easier and understandable terms.” (Volunteer 10, PDF)
	“I'm not used to communicating others' results to lay audiences and this has allowed me to practice extracting the key findings in papers and presenting them in a meaningful and easy way. It has also given me experience in non ‘scientific’ writing.” (Volunteer 12, Graduate Student)
	“Volunteering for SCAsource has improved how I frame the information I want to communicate to the general [public]. Before SCAsource, I didn't realise that information needed to be presented in a different order and structure to ensure maximal understanding by the general public.” (Volunteer 7, PDF)
Connection and confidence in communication with ataxia patients	“Writing articles for SCAsource has helped me put myself in the shoes of ataxia patients. I have been able to better empathize with patients by thinking about articles, how they relate to the situations of ataxia patients, and why patients should care about scientific research. This makes it easier to not only write future articles, but also help me get practice for how to speak with other lay members about science. ” (Volunteer 3, PDF)
	“[Volunteering] has given me more confidence in my ability to communicate to a lay audience through writing.” (Volunteer 18, Consulting Scientist)
	“ [Volunteering] has helped with my confidence in communicating clearly in plain language.” (Volunteer 5, Research Technician)
Strengths of the SCAsource Initiative	
Provides opportunity for	“It has also done a great job of allowing many members of the ataxia research community to get involved.” (Volunteer 3, PDF)

researchers to practice knowledge translation	“[SCAsource has] Provided many opportunities for practice.” (Volunteer 9, Graduate Student)
Comprehensive platform for laypersons to learn about current research ataxia	“I think that having the mix of articles, snapshots and the glossary is great. I think together they all provide a really comprehensive platform for the general public to learn about the current research and background of SCAs.” (Volunteer 7, PDF)
	“I think SCAsource has done a good job at covering current topics and at providing a good platform for scientists to communicate with the SCA community.” (Volunteer 18, Consulting Scientist)
Areas of improvement for the SCAsource Initiative	
More extensive volunteer training	“I think a training module, either a short video or a slide deck, could be made to explain how to properly write a summary for a lay audience.” (Volunteer 3, PDF)
	“I also think more training or guidance should be provided on how to communicate information to patients. As researchers we are used to 'overselling' the translational impact of our research for grant applications and it can be difficult to change tone and communicate to patients in a way that doesn't give false hope or isn't mistaken for medical advice. As scientists I think we need guidance on how to realistically communicate science to patients.” (Volunteer 6, Graduate Student)
Need to improve awareness and visibility	“Visibility. I've only heard about SCAsource through my collaboration.” (Volunteer 17, Other)
	“As SCAsource gains more traction (and philanthropic funding) it would be interesting to explore reporting summaries from NAF conferences or have a social media presence toward in press articles/what is coming down the pipeline.” (Volunteer 1, Principal Investigator)
	“Better PR: linkedin page, facebook etc.” (Volunteer 4, PDF)

Positive feelings about participating in the SCAsource initiative	
	“I really enjoy being part of the SCAsource community and think that it is a great platform for the general public to learn about SCAs. I am very grateful for the opportunity to contribute to this effort.” (Volunteer 7, PDF)
	“I think what [SCAsource is] doing is great and deserves more traction.” (Volunteer 12, Graduate Student)
	“Very valuable contribution to the community!” (Volunteer 16, Principle Investigator)
	“Keep up the good work!” (Volunteer 18, Consulting Scientist)

Table 3.4 Reader themes and representative quotations.

Strengths of the SCAsource Initiative	
Easy to understand content	“Scientific research written in a way that is clearly understandable.” (Reader 29)
	“I really like that difficult topics for non-scientists to understand, such as RAN translation, is explained in a more accessible way to patients.” (Reader 36)
	“Easily written but not to short and not to simplified” (Reader 8)
Accessible resource and information	“Quicker access to information regarding SCA and being able to link to other sites and resources for additional information. Not being a researcher myself, the information is produced in understandable language for the average person.” (Reader 10)
	“[SCAsource has] information regarding up to date research.” (Reader 14)
	“ Very good communication channel for ataxia research” (Reader 20)
	“It is an excellent resource” (Reader 29)
Information on ongoing research	“Good summaries, research articles / to see some progress in the research” (Reader 8)
	“I like to hear about the research that is currently ongoing.” (Reader 3)
Areas of Improvement for the SCAsource Initiative	
More information about research that readers can participate in	“More information about research studies that people can participate in, and how they can participate.” (Reader 36)
	“Some more information about the studies, e.g. READISCA , etc. Like an overview to get even more people involved” (Reader 8)

More information on ongoing research, who is doing research	“A round-up of EVERY current (and past) research project.” (Reader 3)
	“Timeline of what is going on in the ‘research’ world” (Reader 8)
	“[I would like] pictures of the authors” (Reader 5)
More frequent updates	“Should be updated more frequently.” (Reader 21)
Better advertisement of content	“The only time I see new articles is when random patients post them in the NAF facebook groups! You should have a facebook page” (Reader 36)
Lack of suggestions for improvement	“I don't know. Everything seems correct.” (Reader 4)
	“Nothing - I think it is excellent” (Reader 29)
	“It’s great” (Reader 12)
Appreciation for SCAsource as a Resource	
Gratitude for the creation of SCAsource	“Keep on keeping on. And remain upbeat about it.” (Reader 3)
	“I really like to see that the content is posted regularly and I really hope that the site will stay.” (Reader 8)
	“Thank you for your work.” (Reader 33)

Figures

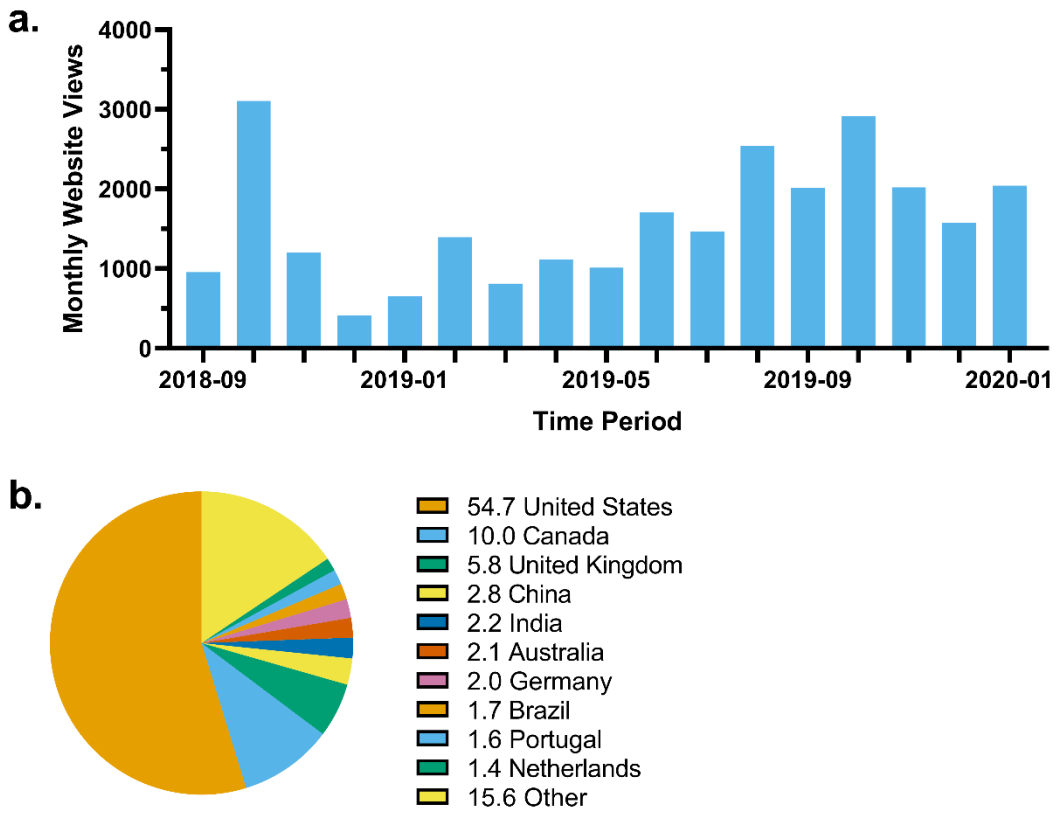

Figure 3.1 SCAsource website visit statistics. (A) Total website views of SCAsource.net per month. Time period ranging from September 2018 to January 2020. (B) Country of origin of SCAsource viewers. Top ten individual values displayed with representative percentages.

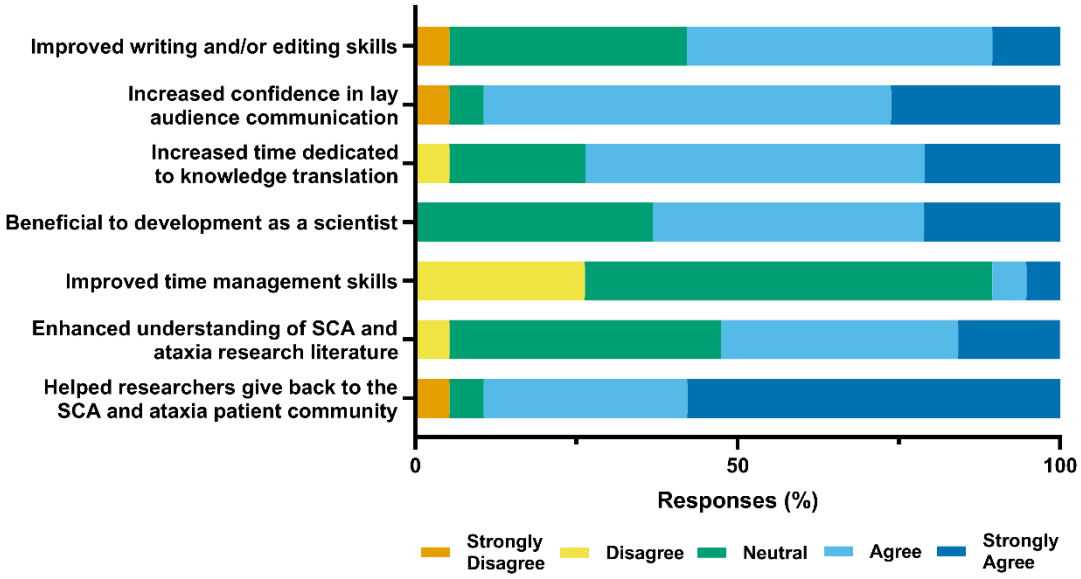

Figure 3.2 Contributors self-reported outcomes of volunteering for SCAsource. Respondents were asked to rate their agreement about whether volunteering for SCAsource resulted in the above statements using the indicated 5-point Likert-type scale.

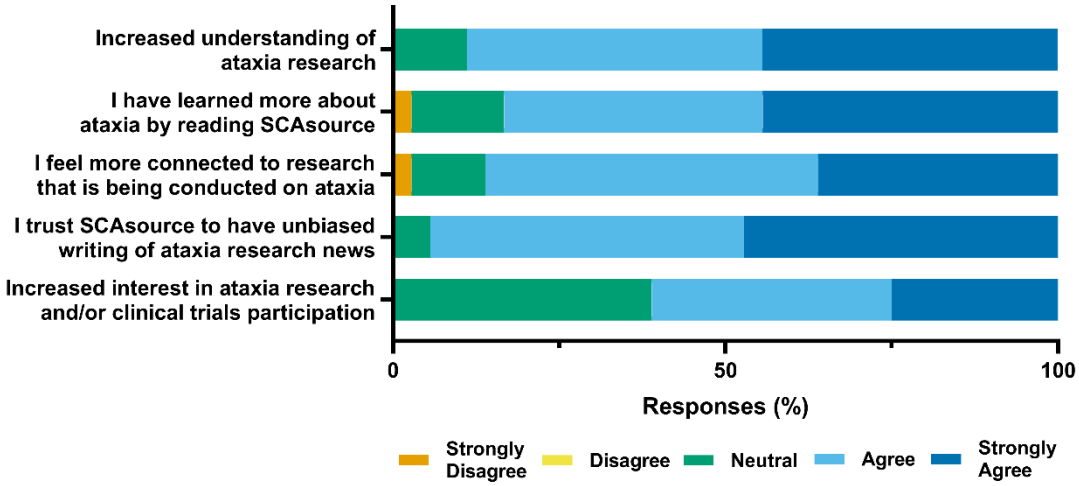

Figure 3.3 SCAsource reader self-reported outcomes. Respondents were asked to rate their agreement about whether reading SCAsource content resulted in the above statements using the indicated 5-point Likert-type scale.

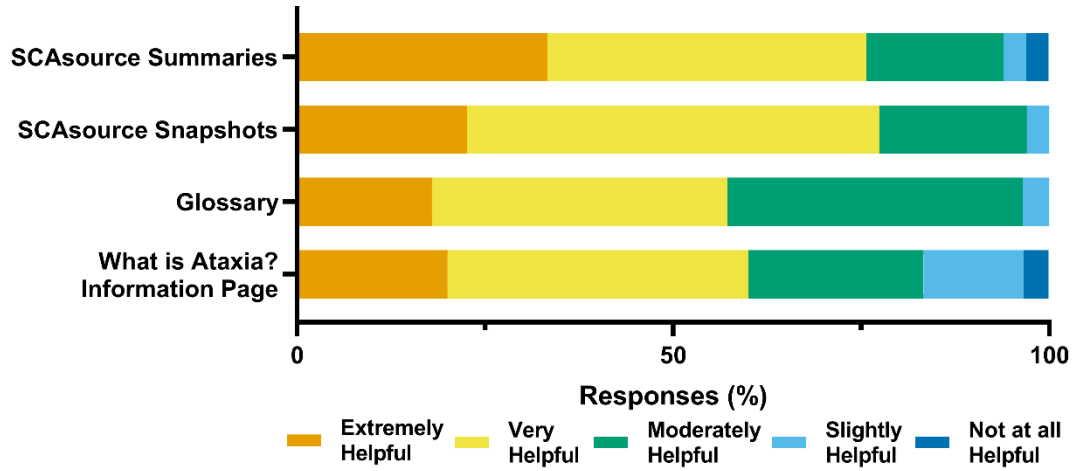

Figure 3.4 Reader helpfulness ratings of SCAsource content. Respondents were asked to rate the helpfulness of four content types of SCAsource; Summaries, Snapshots, the glossary, and the “What is Ataxia?” information page. Responses were given with the indicated 5-point Likert-type scale.

Chapter 4: When the labs closed: graduate students' and postdoctoral fellows' experiences of disrupted research during the COVID-19 pandemic

The material in this chapter is a reprint of the following publication:

Suart, C., Nowlan Suart, T., Graham, K., & Truant, R. (2021). When the labs closed: graduate students' and postdoctoral fellows' experiences of disrupted research during the COVID-19 pandemic. *FACETS*, *6*(1), 966-997. doi: 10.1139/facets-2020-0077

Changes were made in the following publication for continuity and formatting.

Contributions to Publication

CS was first author of this manuscript and contributed 85% of all efforts relating to this project. CS conceived and designed the study. CS and TNS performed the experiments/collected the data. CS, TNS, and KG analyzed and interpreted the data. CS wrote the initial manuscript. KG, TNS, and RT edited the manuscript. Funding for this work was obtained by RT and CS.

Implications of Work

The COVID-19 pandemic turned the world on its head, with laboratories worldwide closing and in-person research being put on hold (230). Similar to many graduate

students, this disruption fundamentally changed the trajectory of my graduate studies. In the initial weeks of the pandemic, there was a focus on transitioning undergraduate student learning from in-person to virtual delivery (231,232). However, there was limited discussion about supporting research-focused graduate students and postdoctoral fellows (233,234).

This publication was one of the first in-depth examinations of how the COVID-19 shutdown impacted graduate students and postdoctoral fellows. We focused on trainees located in Canada completing laboratory-based research. Through a national online survey, we captured a snapshot of the pandemic experiences of research trainees across Canada, as well as identified areas of concern and potential support for graduate students and postdoctoral fellows. From this data, we outlined a series of best practices for widespread laboratory closures for use in future pandemics or natural disasters.

As we were one of the first studies focusing on graduate student and postdoctoral fellow researchers during the COVID-19 pandemic, this work laid the groundwork for several other studies from our group and others (235–239). The high number of citations this work has received since its publication underscores the impact and significance of this study. The beginning of the pandemic was a difficult time for me personally and professionally, I am grateful that work like this with such a positive impact on the academic community could arise from such a challenging period.

Since its publication in June 2021, this manuscript has been cited 30 times.

When the Labs Closed: Graduate Students' and Postdoctoral Fellows' Experiences of Disrupted Research During the COVID-19 Pandemic

Celeste Suart[1], Theresa Nowlan Suart[2], Katherine Graham[1], and Ray Truant[1*]

[1]Department of Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Ontario, Canada

[2]School of Medicine and Faculty of Education, Queen's University, Kingston, Ontario, Canada

*Corresponding author

Celeste Elisabeth Suart - Address: HSC4N54, 1200 Main Street West, Hamilton, Ontario, Canada L8N 3Z5 Email: suartce@mcmaster.ca

Theresa Nowlan Suart - Address: 80 Barrie Street, Kingston, Ontario, K7L 3N6. Email: theresa.suart@queensu.ca

Katherine Jean Graham - Address: MDCL 2310- 1280 Main Street West, Hamilton, Ontario, Canada L8N 3Z5 Email: grahak9@mcmaster.ca

Ray Truant - Address: HSC4N54, 1200 Main Street West, Hamilton, Ontario, Canada L8N 3Z5 Email: truantr@mcmaster.ca.

Abstract

Government imposed lockdown measures in response to the COVID-19 pandemic resulted in widespread laboratory closures. This study aimed to examine the impact of this disruption on graduate students and postdoctoral fellows completing laboratory-based research in Canada. We used an anonymous online survey and semi-structured interviews to document the experiences of graduate students and postdoctoral fellows during laboratory closures and following the transition to working from home. We employed a mixed-method approach using survey and interview data to identify shared experiences, concerns, and supports. The emotions reported by respondents at different points during laboratory closures align with the Kübler-Ross model of grief following change. Respondents describe closure processes as chaotic and confusing, primarily resulting from inconsistent communication. Respondents reported increased indications of distress while working from home. Concerns about how COVID-19 might impact trainees were identified, including decreasing competitiveness of applicants while limiting future employment opportunities. Finally, we outline five types of supports which can be implemented by supervisors and administrators to support graduate students and postdoctoral fellows to return to the laboratory. Overall, we document shared experiences of respondents during the COVID-19 laboratory shutdown and identify areas of improvement in the event widespread laboratory closures occur in the future.

Introduction

In spring 2020, researchers worldwide experienced an unprecedented wave of laboratory closures in response to the COVID-19 pandemic. In mere weeks, nearly all research was put on pause to prevent further spread of SARS-CoV-2 (230).

Widespread closure of laboratories was unprecedented. Research laboratories have had emergency shutdowns following natural disasters before, such as hurricanes, floods, and earthquakes (240–243). However, these shutdowns differ from the COVID-19 laboratory shutdown on two key factors. First, most natural disasters are geographically contained, as opposed to impacting a worldwide population. Second, although catastrophic, natural disasters occur over a finite amount of time. Following a hurricane or earthquake, researchers can begin to make plans for what is necessary to reopen. Closures due to COVID-19 did not come with this timescale, with many not knowing when they will be able to return to pre-COVID level operating capacity.

Researchers and institutions had to react quickly to close laboratories, doing such varied tasks as freezing samples, culling animal colonies, and moving conferences online (230,244,245). Universities rapidly shifted course content online (231,232). However, the initial focus of supporting principal investigators to close their laboratories and helping undergraduates transition to online learning left many graduate students and postdoctoral fellows feeling like afterthoughts in the early days of COVID-19.

More recently, there has been increased awareness of how the COVID-19 research shutdown will impact graduate students and postdoctoral fellows (234,246,247). Most of this work has focused on using past data about this population to predict what difficulties and challenges they will experience due to laboratory closures. Some groups have asked graduate students directly what their concerns are and what supports they require, including work from Australia showing an increase in financial hardship amongst PhD students at the University of Sydney (233).

The purpose of this study was to examine the impact of research disruption during the COVID-19 pandemic on graduate students and postdoctoral fellows completing laboratory-based research in Canada. We did this through a national online survey asking respondents about events surrounding laboratory closures, activities completed while working from home, and their concerns about how COVID-19 will impact them going forward. Our aim was to identify areas of support needed by graduate students and postdoctoral fellows during the COVID-19 pandemic, as well as support needed once the pandemic dissipates. We also wanted to identify best practices for widespread laboratory shutdowns that could be used if similar situations arise in the future. In addition to identifying these supports and best practices, we have documented the stages of grief experienced by graduate students and postdoctoral fellows in response to the COVID-19 laboratory closures.

Methods

Ethics Approval

The study protocol was approved by the Hamilton Integrated Research Ethics Board (HiREB) under project number 10832. Following the recruitment of potential interview participants, a protocol amendment was made to have an additional interviewer, as the primary interviewer had a conflict of interest with two participants. Correspondence with HiREB indicated a formal addendum was not required. Instead, a note to file was added to the study file to document this protocol modification.

Study Design, Participants and Recruitment

We used a convergent mixed-methods research approach, integrating quantitative and qualitative responses from an anonymous online survey and qualitative responses from semi-structured interviews. Mixed-methods research involves the collection of both quantitative and qualitative data, with the aim that the integration of data will yield greater insight than each dataset could provide individually (248). We selected this method due to the emerging nature of the pandemic. As there has not been a pandemic of this scale requiring widespread laboratory closures before, there was limited past literature we could draw upon to inform a theoretic basis for this study. For this reason, a mixed-methods research approach allowed for a holistic viewpoint through the comparison of quantitative and qualitative perspectives (249,250). The philosophical underpinning of mixed-methods

research, pragmatism, also aligns with our research focus as it emphasizes the understanding problems and identifying solutions (251).

Two means of data collection were used: an anonymized online survey and an optional follow-up one-on-one virtual interview. The target population for this study was all persons who: (i) are a graduate student or postdoctoral fellow in Canada, (ii) engage in laboratory-based research, (iii) had their research stopped or paused by the COVID-19 pandemic. There were no inclusion or exclusion criteria based on age, ethnicity, disability, gender, or race.

The online survey was promoted via Twitter and email. For email advertisements, the investigators contacted coordinators of email subscription lists from across all Canadian provinces, including departmental administrative staff, graduate student associations, postdoctoral fellow association, and professional academic organizations. These individuals or groups were selected due to their ability to share study information widely with graduate students and postdoctoral fellows. Midway though the study period, a second set of emails were sent to regions that had a low survey response rate.

The online survey was administered through LimeSurvey, taking approximately 30-45 minutes to complete (S1 Material). Participants contacted by email received a letter of information about the study in Portable Document Format and a link to access the survey. Participants contacted via Twitter were provided a link to access the survey, where an electronic version of the letter of information was provided

prior to obtaining consent to participate. All survey questions were optional, with respondents permitted to skip any questions they preferred not to answer. The online survey was open from April 27, 2020 to June 8, 2020, with 315 respondents completing at least one section of the survey.

At the end of the survey, participants could opt-in to participate in one-on-one virtual interviews and/or in follow-up surveys in a year or more time as the pandemic unfolds. Those interested in participating in virtual interviews were sent a separate letter of information outlining the survey protocols.

Semi-structured interviews were conducted from May, 11 2020 to June 8, 2020 with 18 participants via Zoom, a video conference software that allows for the recording of meetings. Interviews lasted between 30 minutes to 1 hour (S2 Material). Participants' cameras were turned off during the interview process. Following the transcription of interviews, video recordings were deleted.

Data Analysis

Following our mixed-methods research design, both qualitative and quantitative datasets were analyzed in parallel (249,250). Survey and interview data were formatted and transferred to the qualitative data analysis software MAXQDA (VERBI GmbH, Berlin, Germany). Descriptive statistics were generated for both data sets. Quantitative data was entered into GraphPad Prism 8 (GraphPad Software, San Diego, USA) for analysis and formatting. Two-sided Fisher's exact test was used for contingency table statistical analysis.

A thematic analysis was conducted of the narrative feedback from the surveys (252). Themes were discussed and refined by two researchers. The interview transcripts were then analyzed using these same themes, as the interviews were designed to drill down into information provided on the surveys. Data from interviews was used to (i) confirm themes from the survey and (ii) to provide more specific details on individuals' experiences. Beyond information on specific lab shut down requirements (for example, differences between animal labs and labs where experiments can be more abruptly halted, such as where tissues samples can be frozen for long term storage), no new themes emerged. Data from individual interviews did not encompass all themes, but collectively, all themes were addressed. The researchers analyzing the data debated the granularity of themes. More granular themes were more useful and provided a clearer picture of the survey data, while more general categories were more useful when considering the interview data collectively. With these caveats, there were no noteworthy discrepancies between the two data sets. These themes were given to an independent third investigator to ensure identified themes could be subsequently found by someone who had not previously seen the data. A full list of themes can be found in Supplementary Table 3. While the relative prevalence of themes was taken into account, code frequency was not counted due to previously documented limitations of quantizing narrative accounts of experience; implying certain lived experience hold greater significance due to magnitude, that frequency may reflect

a respondent's willingness or comfortability discussing a subject rather than prevalence, and the loss of contextual nuance (252–255).

As was expected, some of the data collected in the interviews was highly specific to individual circumstances. While this did not result in additional themes, this information is important to consider. It draws attention to the fact that laboratory shutdown and reopen protocols must account for local, specific circumstances. While generalizations can be made, there is no one-size-fits-all laboratory shutdown or reopening template. All plans must account for laboratory-specific scenarios. Integration of qualitative and quantitative datasets was achieved through a side-by-side comparison approach within the results and discussion, focusing on convergent and divergent findings from these comparisons (249,256).

Results

Respondent Characteristics

The online survey was completed by 315 respondents (Figure 4.1). Biology (30.2%) and Health Medical Sciences (19.4%) were the most reported respondent area of research (Figure 4.1a). Eight provinces were represented, with the majority from Ontario (34.9%) and Quebec (17.1%) (Figure 4.1b). Most respondents lived with at least one other person while working from home, with only 17.6% of respondents living alone (Figure 4.1c). Slightly less than half of respondents lived with a partner or spouse (44.1%) and 23.9% reported living with parents (Figure 4.1c). Half of the respondents were female, 18.4% male, and 1.2% were non-binary

or genderfluid (Figure 4.1d), with just over a quarter of respondents (27.9%) not disclosing their gender. Doctoral (PhD) students made up 37.5% of respondents, with Master's students representing 21.6%, postdoctoral fellows representing 14.9%, and 26% not disclosing their position (Figure 4.1e). There was a fairly even distribution of graduate student respondents with regards to degree progress, with fewer students in the process of defending their thesis (Figure 4.1f). Postdoctoral fellow respondents ranged in experience from less than 12 months to greater than 48 months in their current position (Figure 4.1g).

A slight majority of respondents (59.6%) had previously published research articles (S4 Table). Postdoctoral fellows were more likely than graduate students to be looking for their next academic position, with 57% of postdoctoral fellows seeking a new position compared to 28% of Master's and 23% of PhD students (S4 Table).

The 18 interview participants reflected general overall demographic characteristics of survey respondents (S5 Table). Most interviewees were female (66.6%), PhD students (72.2%), and conducting either biology (38.9%) or health and medical science research (33.3%) (S5 Table). Four Canadian provinces were represented, with most interviewees being from research institutions in Ontario (50.0%) or Quebec (38.9) (S5 Table). Similar trends were seen in degree progress, the number of months in a postdoctoral position, and those seeking new academic positions (S5 Table).

The Transition from Research to Social Distancing

We asked survey respondents who made the decision to pause experiments or close down laboratories. Seventeen percent reported they personally made the decision to stop experiments before their laboratory was closed (Figure 4.2a). Twenty percent had supervisors who closed their laboratories prior to an official shutdown (Figure 4.2a). Of the remaining respondents, 45.6% experienced closures decided by their department, research institute, faculty, or university (Figure 4.2a). Most respondents completed their final experiments in March 2020, with 68.4% ending in between March 8, 2020 and March 21, 2020 (Figure 4.2b). Only 13.4% came from laboratories with standard operating procedures (SOPs) for quickly shutting down the laboratory created prior to the COVID-19 pandemic, with an additional 18.1% laboratories creating a shutdown SOP in response to the pandemic (Figure 4.2c).

Respondents noted a lack of clear and consistent communication between supervisors, administration, and trainees, leading to a chaotic and confusing shutdown experience. Changes in protocol happened quite suddenly, as two respondents explained:

“One day, we were told that we could continue recruiting human subjects; the next, everything was to be shut down.” (Survey ID 770)

“After a week of emails saying like, ‘We're open. We're open. We're open.’ [...] And then that night around 6:30 PM, after getting an email at 3 p.m. saying ‘We're open’, we got an email saying ‘Gotcha. Campus is closed’.” (Interviewee 6)

There were also discrepancies among people in positions of power in how they reacted to the impending shutdown. This led to graduate students and postdoctoral fellows discussing the situation amongst themselves, increasing their anxiety as many did not have the positional power to enact change at the laboratory or institutional level:

“Some people in charge were behaving like this was a minor inconvenience and others were behaving like this was an apocalypse, you know? So, I think having those kinds of contradictory messages from people in charge was difficult.” (Interviewee 4)

“There was discussion and there was lots and lots of uncertainty and anxiety, I would say, from myself and my peers. Looking towards our supervisor was not very helpful, as I felt that we were more informed about what other institutions were doing than they were.” (Interviewee 11)

Concerning the logistics of laboratory and project shutdown, respondents reported multiple steps to pause projects including: backing up data, setting up remote servers to access data, discontinuing ongoing experiments, freezing samples for indefinite storage, culling animal colonies to reduce numbers or sacrificing animals early to obtain data, discarding samples that could not be stored long-term,

securing equipment and biohazards safely, rescheduling or cancelling in-person meetings with human participants, cleaning laboratory space, testing the back-up power supplies to key equipment (such as freezers), turning off non-essential equipment, and the physical locking up the laboratory. Twenty-nine percent of respondents helped shut down others' projects in addition to their own (Figure 4.2d). A respondent's academic position did not significantly impact the likelihood of assisting in other shutdown activities outside of their project (S6 Table, Fisher's exact test, P=0.2896).

When asked if, in hindsight, they would change anything about the shutdown procedure, respondents discussed three main things they would do differently. First, they would stop experiments sooner out of their own volition rather than being abruptly cut off by the university. Second, they would want "more clear communications from everyone involved" (Survey ID 704). Third, they would have brought more things home with them from the lab, including personal belongings, data, technology, and print resources. Many did not initially take these items as they "did not think [they] would be locked out so long" (Survey ID 156). This also included setting up remote access to data and laboratory information.

A slight majority (63.7%) of laboratories had a uniform closure, meaning all students and fellows stopped experiments at approximately the same time (Figure 4.2e). A similar trend was also reported at the departmental level, with most (70.1%) laboratories closing in unison (Figure 4.2e). A frequent reason cited for a staggered closure of laboratory experiments was differences in ease of pausing

experiments. For example, some respondents recognized that animal model research might take longer to pause:

“Those who had to finish animal data collection went into lab while others started working at home. It made a lot of sense.” (Survey ID 158)

“My colleague was in the middle of an animal experiment and had she terminated the experiment early, she would have had to sacrifice animals without collecting any data, rendering those animals a waste. I am glad she continued the experiment until the planned end-point, thereby not having to use any additional animals.” (Survey ID 188)

Overall, respondents who started to work from home while their colleagues continued working in the lab had a mix of responses to the situation. Some wished they could have continued working for longer, feeling “Frustrated and angry that [colleagues] would complete their research while I had to start over” (Survey ID 183) or that “It felt unfair and I was a little jealous” (Survey ID 253). These sentiments of jealousy and frustration were accompanied by statements of belief that they were falling behind by losing research time. Others were upset that they specifically had been asked to go home first, as this was interpreted to mean their project had “lower apparent priority” (Survey ID 117) compared to others in the laboratory. There were also feelings of concern for colleagues who continued working, as one respondent explained:

"It was also worrying to see others still complete work and putting themselves in harm's way during a pandemic to ensure they could actively finish their experiment." (Survey ID 18)

Conversely, respondents who continued working longer than their colleagues reported feelings of anxiety and guilt. Some felt "guilty that I was putting others at risk" (Survey ID 22) by continuing to work in the lab and that the concern of their colleagues made them feel more anxious. As summarized by one respondent, "I was the one working. And felt like I was doing something wrong" (Survey ID 325).

Respondents who experienced more uniform laboratory closures had different sets of reactions to the research shutdown. Similar to those who had an uneven closure, respondents reported feeling "anxious because it was really starting to show the reality and seriousness of the situation" (Survey ID 284). This anxiety stemmed from realizations that COVID-19 was significant enough to warrant large scale closures or generalized anxiety, rather than citing concern about their safety or the safety of colleagues as expressed by respondents who experienced staggard closures. There were also conflicting feelings of isolation and unity. On one hand, respondents reported feeling "Lonely and sad. I really miss being around my peers" (Survey ID 425). This stemmed largely from losing in-person social interactions. On the other hand, respondents said "it created a sense of solidarity for me. Everyone was working together to try and keep people safe" (Survey ID 533). Others cited a uniform closure as bringing an end to the confusion and mixed messages they experienced prior to the shutdown, "I think I felt a bit relieved when

all the labs finally shut and I knew that everyone was at home. It just meant that all the uncertainty of when the labs were going to close was over and everyone was now on the same page" (Survey ID 767)

We asked respondents to identify if they received any pressure to continue experiments prior to receiving an official shutdown directive from their research institution, and, if yes, the source of this pressure. Many respondents indicated that they received no pressure to continue from their supervisor (65.6%), peers within the laboratory (74.4%), or peers external to the laboratory (84.0%) (Figure 4.2f). Those who were pressured to continue experiments were more likely to be pressured by individuals in their laboratory group, with one third being pressured by supervisors & one quarter pressured by peers within the laboratory (Figure 4.2f).

Some respondents who experienced external pressure said their supervisor "does not believe COVID is a very serious issue and that responses have been an over-reaction" (Survey ID 265) or that they "kept saying things like 'you can't just STOP research'" (Survey ID 364). For others who had peers who "suggested that we were overreacting" (Survey ID 255) or who "felt like the pandemic wasn't super serious" (Survey ID 515), these respondents would question whether shutting down laboratory experiments was the best decision.

A much different trend emerged when respondents were asked about the pressure they put on themselves to continue research: 70.7% of respondents reported some level of internal pressure to continue working (Figure 4.2F). This is consistent with

known levels of stress associated with the ‘publish-or-perish’ culture in academia (38,39,257–259). Respondents described fear of losing research time and data, often tied to a fear of not being able to graduate or submit a manuscript:

“My thesis is due at the end of the summer. I was scared because even if research were to have started up again, I lost my window of time where I could have continued research. At this point, I just have to write a thesis with the data I have.” (Survey ID 73)

“I am losing a lot of valuable data collection time and am concerned I won't finish on time to graduate.” (Survey ID 417)

“The days prior to the shutdown were filled with some pressure because I was trying to finish experiments that would provide data for an upcoming manuscript. My hope was that I'd get the data I needed and then go home and start writing the paper.” (Survey ID 71)

Others explained they felt self-conscious stopping work when peers were working, worried that they would be perceived as less hard working or as lazy.

Following laboratory closures, most respondents (79.2%) remained in the same city in which their laboratory is located (Table 4.1), with the most common explanation being that it is the location of their full-time residence. Other reasons to remain included “not wanting to do unnecessary flying” (Survey ID 99), international flights being cancelled, and not wanting to put family or friends at risk by traveling from an area with a high incidence of COVID-19. For the fifth of

respondents who relocated to another city, most cited moving to be with family as a primary factor, as they lived by themselves and did not want to be alone or because they wanted to move to “an area with fewer cases and less dense population” (Survey ID 739). Some respondents noted they otherwise may not have moved, however, they were away when their laboratory shut down and they did not return:

“I had gone home to visit my parents for a weekend, and they live in another city, and I thought it was just going to be for a weekend, but then the conversation [concerning laboratory closures] shifted over the course of the weekend. So instead of coming back to the big city and the densely populated area, I stayed behind.” (Interviewee 2)

Working from Home during Social Distancing

Following the closure of the laboratory workspace, 48.6% of respondents had individual workspaces in their homes, while 31.0% shared workspace with others in their household (Table 4.2). 20.4% of respondents did not have a dedicated workspace in their home (Table 4.2). 21.9% of respondents were taking one or more courses as part of planned studies which were transitioned online (Table 4.2). Approximately a third of respondents had one or more projects in the process of peer review (Table 4.2).

Respondents completed several activities while working from home, which we classified as being directly related to COVID-19, self-care, research, or household

maintenance (Figure 4.3, Tables 4.3-6). In addition to descriptive reporting of activities by all respondents, we also stratified respondent responses by gender and academic position (S7 and S8 Tables). Differences between subpopulations was determined through Fischer's exact test, with more differences in activities emerging between graduate students and postdoctoral fellow respondents compared to female and male respondents (S7 and S8 Tables).

More respondents reported participating in COVID-19-related activities that directly impacted their family or friends as opposed to the public at large. For example, 76% of respondents indicated sharing accurate information about COVID-19 with family and friends, compared to 19% sharing the same information with the general public (Figure 4.3a, Table 4.3). Other COVID-19-related activities included donation of personal protective equipment (10%), volunteering to support COVID-19 research (11%), and supporting others in quarantine (45%) (Figure 4.3a, Table 4.3). Significantly more female respondents reported collecting or donating personal protective equipment or other supplies to local hospitals compared to male respondents (S7 Table, Fisher's exact test, P=0.0466). Compared to postdoctoral fellow respondents, significantly more graduate student respondents reported completing tasks or errands to support family, friends, or others in quarantine (S8 Table, Fisher's exact test, P=0.0085).

Respondents reported high levels of self-care activities while working from home (Figure 4.3b, Table 4.4). Many prioritized connecting with family and friends virtually, with 84% connecting by video chat, 86% using a text-based medium such

as email or texting, and 80% using phone calls (Figure 4.3b, Table 4.4). Exercising either indoors or outdoors was also frequently reported (85%) (Figure 4.3b, Table 4.4). While 74% respondents returned to previous hobbies or skills, 43% of respondents said they began developing a new hobby or skill while working from home (Figure 4.3b, Table 4.4). Significantly more graduate student respondents reported developing a new hobby or skill compared to postdoctoral fellow counterparts (S8 Table, Fisher's exact test, P=0.0051). Other self-care activities with lower levels of reporting included establishing a new routine (48%), meditation or mindfulness (30%), and attending virtual religious or spiritual services (9%) (Figure 4.3b, Table 4.4).

Despite being away from the laboratory environment, respondents continued to participate in several research-related activities, the most common being reading the literature (85%), virtual lab meetings (82%), and analyzing data gathered prior to shutdown (61%) (Figure 4.3c, Table 4.5). Writing-related activities such as drafting manuscripts (53%), designing scientific figures (42%), and writing thesis chapters (33%) were reported (Figure 4.3c, Table 4.5). Slightly less than half (45%) of respondents attended virtual scientific meetings, conferences, or seminars from home (Figure 4.3c, Table 4.5). Other respondents did activities to help prepare for after the pandemic, such as creating strategic plans for future experiments (44%) or updating their curriculum vitae and/or LinkedIn profile (43%) (Figure 4.3c, Table 4.5). Five of the eight significant differences identified between postdoctoral fellow and graduate student respondents' activities reported were research-related

activities. Unsurprisingly, significantly more graduate students reported writing thesis chapters than postdoctoral fellows (S8 Table, Fisher's exact test), P<0.0001) Significantly more postdoctoral fellow respondents reported writing draft manuscripts (P=0.003), working on paper revisions (P=0.0011), completing online training (P=0.0161), and updating their curriculum vitae and/or LinkedIn profile (P= 0.032) (S8 Table, Fisher's exact test).

There were high levels of reported household maintenance activities, including cleaning tasks (94%), cooking meals for self (89%), cooking for others (70%), and completing necessary excursions such as grocery shopping (80%) (Figure 4.3d, Table 4.6). Significantly more female respondents reported completing necessary excursions as an activity compared to male respondents (S7 Table, Fisher's exact test, P=0.0303). In terms of caregiving, 10% of respondents reported caring for children, while 3% reported caring for dependent adults (Figure 4.3). More postdoctoral fellow respondents reported caring for children compared to graduate student counterparts (S8 Table, Fisher's exact test, P=0.0061). 39% of respondents reported caring for pets (Figure 4.3d, Table 4.6). Overall, more than half of respondents thought there was an even distribution of labour in their household (66.1%) (Table 4.7). Slightly more men than women reported that household labour was evenly distributed (76.6% vs 63.2%), however this trend was non-significant (Table 4.7, Fisher's exact test, P=0.11). These respondents described “dividing tasks so that everyone plays a role and contributes to household chores” (Survey ID 87).

Others reported one or more members of the household intentionally took on more household responsibilities from others:

“My partner isn't employed right now so he does more than half the chores because he has more time than me.” (Survey ID 29)

“Some household members have chronic health issues and aren't able to do as much.” (Survey ID 462)

However, some respondents had an uneven distribution of household labour that they were dissatisfied with, describing a continuation or amplification of an imbalance which existed prior to the COVID-19 pandemic:

“Some gender roles are hard to escape and I find myself, now that I am always home, picking up even more of the slack than before.” (Survey ID 248)

“Though my partner and I both work from home, I still feel like a lot of home duties fall on me. I do 80% of the cleaning and cooking--though this is not much different prior to COVID.” (Survey ID 741)

Respondents were asked to rank how frequently they experience, if at all, a variety of symptoms of distress while working from home (Figure 4.4). We used a list of distress symptoms (Items 1-8, S9 Table) previously developed by the National College Health Assessment Survey II (NCHA II) (260). Additional items (Items 9-16, S9 Table) were included as there was anecdotal reporting of these symptoms by graduate students through social media. The most reported symptoms related

to attention, including lowered productivity and difficulty focusing on tasks (Figure 4.4). Other symptoms with high incidence included difficulty getting out of bed, exhaustion not related to physical activity, and feeling overwhelmed (Figure 4.4).

A greater proportion of female respondents reported symptoms of distress than male respondents (S9 Table). However, only two distress items had significant differences between men and women; feeling overwhelming anxiety (Fisher's exact test, P=0.0067), and being easily annoyed or irritable (Fisher's exact test, P=0.0029) (S9 Table). This trend is consistent with past findings and literature showing women are more likely to report symptoms of distress (261–263).

Respondents were asked to identify their three biggest barriers to getting work done at home, to which four main barriers were identified. The first barrier was technical issues, which primarily stemmed from lack of access to stable, high speed internet. Other issues in this category included not having enough computer processing power to run analyses and access to software. The second barrier was distractions in the home, such as noise, other household members, and household chores that are not present in the laboratory:

“So if I just get up to go grab a glass of water, then I'll see something and I'll fix it. Or oh, there's a little bit of dishes. I'll start doing them and I'll start doing other things, and I'll never go back to work. So when I work in the lab and in my office at the desk, there's nothing else.” (Interviewee 14)

Respondents with children also cited childcare as another distracting factor, as one respondent put it “[My daughter] is only 15 months so she requires a lot of hands-on attention, so my husband and I take turns watching her so we only work for 2-2.5 hours/day” (Survey ID 137).

The third barrier identified was motivation, or lack thereof. Respondents had difficulty starting tasks, focusing on tasks, and finishing activities. Some attributed this to the lack of an impending deadline, as “nothing seems pressing and I sometimes genuinely do not feel like working” (Survey ID 129). Others felt that their “research is less relevant now” (Survey ID 52), and since they were unable to do experiments, they lacked motivation to do other activities.

The fourth barrier was mental health, with either new anxiety or depression developing, or previous conditions worsening with the pandemic shutdown. As one respondent explained, “managing my anxiety and depression during this uncertainty has left very little energy to focus on work” (Survey ID 311). Thus, their main activity during this period was taking care of themselves. Oftentimes, lack of motivation and mental health barriers compounded with one another, as described by one respondent:

“My brain seems to just shut down all the time, and I have a hard time controlling and coming out of it. I just feel so overwhelmed thinking I have so much to do that I don't do anything and then I get anxious because I'm afraid that I didn't do enough work.” (Survey ID 562)

We next asked respondents to list three supports they received while working at home, to which five main categories of support were identified. The first support was financial, with respondents citing the “financial security of my stipend” (Survey ID 311), the Canada Emergency Student Benefit, the Canada Emergency Response Benefit, and other sources of monetary support in order to cover costs and “prevent financial anxieties” (Survey ID 48). The second support was social connections, which was described as coming from several sources, including family, friends, a partner or spouse, children, laboratory peers, and pets. As summarized by one respondent, these social connections made them “feel supported and validated in my feelings, and knowing that we're all struggling. Support from friends and peers makes me feel less alone and I know I'm not the only one having trouble with this” (Survey ID 493).

The third support was establishing and maintaining routines during social distancing. Respondents said having routines, either self-imposed or from external sources such as a weekly laboratory meeting, helped with finding motivation, as well as “feeling that there is a rhythm and purpose to my daily life again” (Survey ID 133). Dog-owning respondents cited their pet, in addition to emotional support, also served as an external source to gently force them to maintain healthy routines:

“Having a dog has helped me stay in a normal routine of getting up at a decent time to take her outside and getting out for a walk every day.” (Survey ID 515)
“My dog insists on thrice daily walks, which gets me up and moving. And I find that I get back from walks and I can focus a lot better.” (Interviewee 6)

The fourth support respondents identified was relating to mental health, which mirrors the previously identified barrier. This included professional support, including counselling, therapy, and remote telemedicine services. Other supports included meditation and exercise as means to maintain mental health. As explained by one respondent, “running removes all the excess anxiety and improves my mood” (Survey ID 116).

The fifth type of support came from the respondent’s supervisor or other administrative figure. This included virtual laboratory meetings to implement routine as well as keeping respondents socially “connected to my work and my co-workers” (Survey ID 255). However, most respondents identified supervisors’ and administrators’ understanding, transparency, and emotional support as what they valued the most:

“My supervisor is very supportive not only of my research but also my well-being. He listens and encourages me to take care of my mental health and understands that this social distancing thing is having a pretty big impact on me.” (Survey ID 562)

“[My] supervisor telling the group during lab meeting to focus on health and family and not expecting any productivity at this time.” (Survey ID 87)

“My department chair has been very transparent which has provided clarity and some ease of anxiety.” (Survey ID 195)

"I'd say my supervisor genuinely, she has been incredibly supportive during this time of understanding what it's like to go through this, but also keeping us very aware of decisions that are being made and very realistic." (Interviewee 3)

Concerns and Supports for Returning to the Laboratory

Respondents had a number of concerns that the COVID-19 pandemic could impact them going forward (Figure 4.5). There was a high degree of similarity between quantitative and qualitative data focused on respondents' concerns. These worries tended to fall into three categories: personal, disruption of research activities, and career impacts. A minority of respondents also said they were not very worried about the impacts of COVID-19.

As personal concerns, respondents were worried friends or family members would get sick or die from COVID-19, especially those with underlying health conditions or who were essential workers. Interestingly, respondents were more worried about others contracting COVID-19 than themselves contracting it (Figure 4.5).

Respondents were more concerned about "the impact COVID-19 will have on my long term physical and mental health" (Survey ID 516). Thus, the concern came from the impact of social distancing and working from home in response to COVID-19, rather than concern of contracting the virus. Respondents cited concerns about decreased social interaction while working from home, which left them "feeling lonely and isolated" (Survey ID 394). Some did not know when they would be able to see their family face-to-face again. Others were concerned that this would

negatively impact their ability to make connections with people going forward as "spending so much time in social isolation will just exacerbate" (Survey ID 513) their natural awkwardness or introversion. Maintaining current social connections was also a challenge, as one respondent put it:

"Not being able to physically see people makes it harder to maintain connections. I had a 'COVID' birthday and it felt like I was forgotten by most people, even though a birthday is not a priority in times like these." (Survey ID 37)

A section of respondents was concerned that they would need to delay key life milestones such as getting married, beginning a new job, or starting a family. Often these events were pushed back due to a respondents' graduation date or end of postdoctoral fellowship getting extended due to laboratory closures. One respondent summarized the impact of COVID-19 as follows:

"This situation has screwed up my whole life plan, I just want to scream, I feel like I have no control." (Survey ID 377)

Despite financial help being identified previously as a support by some respondents, 56.6% worried that COVID-19 would impact their personal finances. Some were struggling even with governmental support, while others were worried about the security of their research funding. Increased financial uncertainty was cited as a reason some respondents were choosing to delay life milestones. Others were frustrated that they needed to continue to pay tuition fees, despite not being able to conduct research:

“I am still paying full tuition to sit on my couch and not be allowed into my lab, when that tuition I'm paying is to be a part of a research program, a research program I currently cannot take part in.” (Interviewee 17)

Respondents listed a number of concerns related to their current research activities. Some were worried “that funding for basic research will become scarce” (Survey ID 80) due to the focus on COVID-19 research and the state of the economy. Others were concerned about going overtime on their degree or fellowship due to COVID-19 would impact their eligibility for funding in the future. Traditionally, this would result in reduction or stoppage of stipend money. Although many institutions and funding agencies have announced accommodation for students and fellows for fall 2020, respondents were more concerned about the “availability of funds next year and the coming years, [as] that may actually be an issue” (Interviewee 8). This worry of going overtime or delaying graduation due to decreased research productivity was intertwined in several responses throughout the survey. Some respondents had “cancelled [their] current research topic and forced [them] to have to change it” (Survey ID 664) in response to the laboratory shutdown, modifying their thesis in a way that would forever be impacted by COVID-19. Others lamented canceled travel opportunities for networking and “missed opportunity for international collaboration” (Survey ID 742). As one respondent explained:

“I'm in that crucial new investigator period of my career. COVID represents a year of no conferences, no networking, no data collection... it’s setting everything back.” (Survey ID 203)

Many concerns regarding current research activities connected with concerns about how COVID-19 might impact their careers: 86.4% of respondents were worried about their competitiveness as a researcher, with 36.6% describing themselves as ‘extremely worried’ (Figure 4.5). Many respondents were concerned that their lack of productivity during the laboratory closure period and decreased publications would make them less desirable candidates for future positions. As summarized by one respondent:

“My goal is to become a tenure-track faculty member at a research-intensive university, which is a difficult enough task as is. But I worry that because of this situation, I will either not be productive enough to secure a position, or I will have to prolong my postdoc experience in order to gain enough productivity to be a viable candidate. I also worry that universities will have decreased hiring in the next few years, which coincides with my entry into the academic job market.” (Survey ID 255)

Many respondents were concerned about the availability of employment both within and outside academia in the post-COVID-19 era. Some hope “there are still jobs in academia (or any kind of research) after all the economic fallout” (Survey ID 99). Postdoctoral fellows, in particular, were concerned about universities

freezing hiring for faculty positions. Some respondents had already made the decision to alter their career goals in response to COVID-19:

“I am convinced about leaving Academia.” (Survey ID 113)

“Before COVID, I was gaining momentum in my project. I was deciding between transferring from MSc to PhD, but after COVID I lost this motivation entirely. I now have decided to finish with an MSc and hopefully find a job afterwards.” (Survey ID 763)

“I feel like the time away from [the lab], whether this is good or bad has maybe made me cooled off a little bit and like feeling more, I don't know, further from science and thinking that maybe that's not bad.” (Interviewee 4)

Respondents had a number of ideas when asked about what supports would help them transition back to laboratory work post COVID-19 which we categorized into five groups: personal protective equipment and protocols, understanding and empathy, guidance and direction, timeline support, and financial support.

The minimum support respondents asked from both supervisors and administration were adequate personal protective equipment and protocols on how to reopen and work in laboratory space. The emphasis was placed on clearly communicating safety procedures and protocols that are put in place, as respondents did not want a similar confusion and anxiety that took place during laboratory shutdowns to repeat themselves.

What respondents wanted most from their supervisors was the first two groupings of support: (i) understanding and empathy and (ii) guidance and direction. First, respondents wanted “understanding I won't be as productive as before COVID for a long time” (Survey ID 458), “reassurance that delays are acceptable” (Survey ID 739), and “emotional support and encouragement” (Survey ID 769). Respondents described wanting their supervisors to be explicit that they do not expect pre-COVID-19 levels of productivity and that they will not be made to feel guilty over lost time. They also wanted “moral support getting back on track with experiments” (Survey ID 123), as respondents are still reeling from the emotional and stressful toll of the shutdown experience. Respondents described hesitancy and fear at returning to a laboratory situation where this flexibility was unlikely to be found:

“My supervisor has zero empathy or tolerance and I’m extremely worried about going back to work with him” (Survey ID 69)

Second, respondents were hoping to receive explicit guidance and direction from supervisors as to where to go with projects once they returned to work. There were frequent descriptions of wanting “clear goals for me to finish my program” (Survey ID 93), “a detailed plan of how to be most efficient with research efforts” (Survey ID 347), and “clear communication” (Survey ID 248). Respondents encouraged the development of a research plan that would limit the potential negative impacts of the laboratory shutdown, get experiments back up and running efficiently, and keep respondents on time in their degree progression. Respondents also wanted supervisors to “acknowledge that the PhD or the master's degree that students had

originally set out to accomplish may not be feasible within our current time frames" (Interviewee 11) and that adjustments would be required.

The supports requested from administration, including departments, faculties, and the university itself, focused more on structural supports including degree timeline and financial supports. Timeline support focused mainly on flexibility. Some students explicitly asked for "flexibility for certain milestones (comprehensive exams, graduation timeline, funding timeline) that allows us to get back to our research without feeling like we need to compress everything into the time that we lost" (Survey ID 92). Others wanted expectations for key requirements to change as extending time in their degree "is something I really don't want to do" (Survey ID 651) and wanted "assurance that I will graduate on time" (Survey ID 583). Respondents had a variety of suggestions for financial support, including increasing fundable periods for all students and fellows, ensuring students who go overtime due to COVID-19 are not penalized financially, lowering the cost of tuition, and increasing financial support for students to purchase software and technology to work partially from home. Respondents also asked that specific guidelines for timeline and financial support be developed for international students and fellows. This was due to international trainees having a unique set of concerns regarding these two items related to Canada's immigration and visa policies, which could potentially change in response to COVID-19.

Grief Response to COVID-19 Laboratory Closure

There was an underlying feeling of grief that permeated throughout survey and interview responses. Respondents lamented the data that was lost, the conferences that might have been, and how this new reality of social distancing and working from home was not something they ever expected. We used the Kübler-Ross model of grief as a lens to view respondents' reactions to the laboratory closures.

The Kübler-Ross grief construct is one of the most well-known models to describe the process of grief (264). Although initially developed to describe how people process the grief that results from terminal illness and death, it has also been used to describe grief from a variety of sources, including job loss, educational reforms, and organizational change (265–268). The Kübler-Ross model outlines five stages of grief: denial, anger, bargaining, depression, and acceptance. The stages described by Kübler-Ross are not a linear process, but can occur simultaneously and in any order (264).

Denial is the disbelief following unexpected and shocking news, which Kübler-Ross and others posit gives individuals time to process (264,269). Anger is when frustration boils over, often due to perceived unfairness of the situation (264). Bargaining focuses on what could have been done differently to change what is happening, even if nothing could have been done to prevent the situation (264). Kübler-Ross described bargaining as the temporary belief that "there is a slim chance that [the person experiencing the change] may be rewarded for good

behavior and be granted a wish for special services", that they will be 'rewarded' for this behaviour and the situation will be better than anticipated (264). Depression is the sense of loss that occurs when the person acknowledges the situation cannot be 'fixed' or glossed over, replaced by a sadness that is often very private (264). Acceptance is learning how to live with the new reality the person finds themselves with, finding a new equilibrium that does not have the same emotional highs and lows of the previous four stages (264). Some scholars suggest 'hope' could be a sixth stage to the Kübler-Ross model, however, the model suggests hope is present throughout all stages of grief and simply reasserts itself during acceptance (264).

Respondents were provided with a list of 37 randomized feeling words, each of which has been previously attributed to a stage of the Kübler-Ross model (270). They were asked if they had experienced any of these feelings during the laboratory shutdown period, while working from home, and when they thought about the future (Figure 4.6). Respondents could also include other emotions they felt during these periods, which were then classified into Kübler-Ross stages based on categorization by Kearney and Clapper (270,271).

Anxiousness was highly reported across all three timepoints, mirroring the symptoms of distress reported in Figure 4.4 (Figure 4.6a). The trend of anxiousness reflects most feeling words in the bargaining stage, showing a decrease in reporting at the second time point and increasing in the third (Figure 4.6a). Conversely, depression stage feelings like "lonely", "discouraged",

“depressed”, or “apathetic” had higher levels of reporting while respondents were working at home compared to other time points (Figure 4.6a). A similar trend was found with “calm”, “contented”, and “easy-going”, three acceptance stage feelings (Figure 4.6a). More subtle trends included the reporting levels of “disbelieving” decreasing at each subsequent time point (Figure 4.6a). Three feeling words with the opposite trend were “anger”, “bitterness”, and “afraid” both of which saw the highest levels of reporting when respondents thought of the future (Figure 4.6a).

When observing Kübler-Ross stages as a whole, rather than individual feeling words, more respondents reported bargaining-associated feelings across all three timepoints (Figure 4.6b). The second most-reported feeling category was depression, which saw an increase in self-reported feelings during the work from home period (Figure 4.6b). The three remaining Kübler-Ross stages have more subtle variations, with overall denial decreasing, anger increasing, and acceptance having a similar trend to depression (Figure 4.6b).

Although the majority of respondent data focused on negative feelings deriving from being in a pandemic, there were small undercurrents of optimism for the future within narrative responses. This overall negativity may be in part due to when respondent data was collected, three months or less following initial laboratory closures. With time and distance from the laboratory shutdown, these may grow further. As succinctly pointed out by one respondent: “I really hope it's all going to be okay” (Survey ID 265).

Discussion

In this study, we assessed the self-reported impact of the COVID-19 laboratory closures on graduate students and postdoctoral fellows. This was done through a mixed-methods research design with online survey data collected from 315 unique respondents and 18 semi-structured interviews. Some data collected was highly specific to individual respondents and laboratories, emphasizing there is no one-size-fits-all protocol for laboratory shutdown or reopening. The distinctive characteristics inherent to each laboratory across Canada will require any plans made to account for their unique context. However, some generalizations can be made, rooted in experiences, feelings, and concerns shared by respondents across the country. These findings also align with those found in a larger nationwide survey of graduate students, which included respondents of non-research based and professional programs (272). A summary of fundamental recommendations derived from our findings are summarized in Table 4.8.

Respondents' experiences of initial laboratory shutdowns were, for the most part, chaotic, confusing, and abrupt. Institutional and laboratory policies changed quite rapidly, including the decision whether to close research laboratories at all. This uncertainty mainly stemmed from a lack of clear, consistent communication from administrators. The lack of consistency in policy within research institutions, as well as between institutions, left many graduate students and postdoctoral fellows feeling anxious and adrift. Much of this is understandable, as administrators themselves were reacting to an unanticipated and emerging situation for which

they did not have prior experience to inform them how to proceed. However, this uncertainty was compounded as information and decisions were released, from administrators to principal investigators to graduate students and postdoctoral fellows. If similar situations arise in the future, minimizing discrepancies in messaging, as well as abrupt changes in policy, will minimize potential harms and stresses on graduate students and postdoctoral fellows.

In terms of the physical closure of the laboratory space, respondents had a clear understanding of what was required to pause their research projects in terms of preservation of data and safety procedures. When asked what they would do differently if they had to repeat the closure experience, most focused on beginning the shutdown earlier and bringing more materials home with them. These recommendations, in addition to a desire for better communication from administrators, stem from an underestimation of the gravity of the COVID-19 pandemic and how long the laboratory closure would last. Many lamented limited access to data and laboratory notebooks. One solution that some laboratories implemented was setting up remote access to laboratories resources, software, and data. Although there was a technological requirement needed to support this remote access, respondents who identified that they were able to access data remotely found it valuable. This strategy could be used by others to pre-emptively prepare for future laboratory closures.

Another factor to consider for future laboratory shutdowns is the decision to end all work at approximately the same time, or allow some laboratory members to

continue working during a partial shutdown. Graduate students and postdoctoral fellows who experienced uniform and staggered laboratory closures had distinct emotional responses to the shutdown. Although both groups experience anxiety, the root of the anxiety came from different sources. For those from staggered closures, this unease came from fear of falling behind in data collection for those who were at home, and fear of putting themselves or others at risk from those who were in the lab. In contrast, respondents from uniform closures cited a realization of the seriousness of the situation as the source of their anxiety. Another key contrast is that respondents from uniform closures reported a sense of safety coming from the solidarity and unity of everyone stopping work at once, which did not occur for those with staggered closures. This suggests that a uniform approach to laboratory closures should be used whenever possible, with exceptions for certain types of experiments which take longer to pause, such as animal model research. Not only will this minimize negative outcomes for graduate students and postdoctoral fellows at the time of the closure, but will prevent a hierarchy between those with ‘high priority’ and ‘low priority’ projects from emerging in the long term.

Overall, research institutions should proactively plan for their future pandemic response, rather than have another reactive situation like that seen with COVID-19 laboratory closures. Developing official guidelines on pandemic responses, similar to other emergency situation response guidelines already in place will help promote consistency in implementation and minimize potential chaos or confusion. It will also reduce the need for abrupt changes in policy and sudden closures.

Graduate students and postdoctoral fellows reported completing a variety of activities while working from home. This included research-related activities, despite not having access to the laboratory space. Although some differences in activities were identified when respondents were divided by reported gender, more significant differences were identified between respondents in different academic positions. Some of these differences between graduate students and postdoctoral fellows may be explained by life stage, such as a higher incidence of postdoctoral fellows reporting childcare responsibilities. Past surveys have identified that postdoctoral fellows are older than graduate students, with many reporting being married or having dependents (273). Differences between graduate student and postdoctoral fellow respondents in research-related activities may reflect the greater level of professional responsibility associated with postdoctoral researchers in laboratories. Understanding differences in activities being completed at home by respondents across different subpopulations can help to identify what kinds of supports to provide in the event of another widespread laboratory closure.

Unlike previous research, 66.1% of respondents believed that there was an even distribution of household labour activities. For some, this distribution was intentional, in order to assign tasks based on free time availability. This was not the case for many respondents who cited gender roles around domestic tasks and caregiving as one contributing factor. This, in part, could explain some of the trends we see, as the majority of respondents did not report childcare responsibilities. The

challenges of parenting while conducting research, especially for female researchers, have been previously documented in the literature and have been cited as a COVID-19 related barrier (274–276).

Although not unexpected, respondents reported high levels of distress while working from home. Compared to past Canadian data using the NCHA II distress items, a greater proportion of male and female respondents reported experiencing these symptoms of distress than reported on past surveys (S6 Table) (277). Respondents are typically asked whether they experienced any of the NCHA II distress items over the past 12-month period. Our data displays a trend of more frequent instances of distress over a shorter period. This aligns with the respondent reports of their own mental health and feelings of apathy being major barriers to getting work done at home. Unlike technological barriers, which for many could be solved with additional financial support to improve technology and internet connectivity, both negative mental health and loss of motivation do not have straightforward solutions. These cause long term impacts for people, even beyond the pandemic. There has been growing concern for lack of mental health services for graduate students and postdoctoral fellows (278,279). The aftereffects of the pandemic may exacerbate this need for increased resources and professional support. Some respondents already reported seeking new or using previously established mental health supports to cope during this time. This, along with social connections with friends or family and emotional support from supervisors, paints

a picture of respondents who are reaching out to a variety of sources to cope with the distress they are experiencing.

When looking at the key concerns of graduate students, many are pre-existing concerns that have been amplified by the pandemic, such as those related to research productivity and career prospects (278). This is consistent with other postsecondary students across Canada, with recent data identifying that 67% of students were very or extremely concerned about their job prospects in the future (280). Many institutions are already scaling back hiring of new academic research positions due to predicted economic uncertainty (281). Due to an already small prospective job pool becoming even smaller as a result of these cuts, this has increased the pressure on graduate students and postdoctoral fellows to “publish or perish”. However, many are currently unable to collect data due to laboratory closures or are working at reduced capacity as laboratories slowly reopen. The pressure to perform in order to secure their financial and academic future has run up against the outside force of the pandemic, which they do not have control over. This lack of agency over when and how they will return to the laboratory can partially explain the high reported levels of distress, as well as the concern that this will decrease their competitiveness as a researcher.

These concerns are also reflected in the support requested from supervisors; understanding and empathy surrounding the return to the laboratory and guidance on how to best approach the return to ensure productivity. As graduate students and postdoctoral fellows are already placing internal pressure and stress on

themselves following laboratory shutdowns, they do not want to receive additional external pleasure from their supervisors. Instead, they want to receive emotional support from their mentor to process and cope with this stress. Respondents also want clear guidance and direction from their supervisors, thereby increasing productivity and data collection to minimize potential negative impacts respondents are predicting the laboratory closure will have on their career. Although both supports will be helpful to graduate students and postdoctoral fellows at large, the authors would also like to acknowledge that these supports will be especially important for those researchers with children. Respondents with childcare responsibilities, primarily women, were a minority in the survey data, however, they had unique challenges trying to balance full-time research and parenting responsibilities. Data has already emerged showing women have begun to publish less and start fewer new projects during the pandemic, with increased caregiving responsibilities being cited as one potential explanation (282). Supervisor understanding and guidance during this period will be key to minimize negative repercussions as a result of researchers with children decreasing research activities.

Other more generalizable COVID-19 related concerns reported by respondents mimic those amongst many Canadians: concerns about maintaining social connectedness, financial worries, and concerns about the health of family, friends, or oneself (283,284). Respondents reported lower levels of concern related to personal finances (56.6%) than the total population of postsecondary students in

Canada (77%) (280). This may be partially explained by respondents receiving stipends and other continued research funding, while the postsecondary population surveyed by Statistics Canada included undergraduate students who do not have these supports. Unlike many Canadians who are struggling to cover living expenses and food costs (285), we only had a handful of respondents cite these as major concerns. This could be in part from differences between our target population and the Canadian population as a whole, as it has been documented that many individuals who are able to attend graduate school have pre-existing economic privileges (286,287). In this sense, most financial concerns were tied to long term outcomes, such as not being able to find employment or provide for family in the future, rather than immediate concerns related to food or shelter. This is consistent with support requested from administration and universities and research institutions, asking for guarantees of long term financial and degree timeline support to minimize these longer-term concerns.

All of this is framed in the context of the emotional response to laboratory closures. Graduate students and postdoctoral fellows were grieving, in a variety of ways, the research that might have been and the loss of the pre-COVID-19 research landscape. Most respondents reported emotions associated with bargaining and depression stages of the Kübler-Ross grief construct, which can inform ways to approach supporting this population now and during the return to laboratories. Kübler-Ross described bargaining as “an attempt to postpone” an inevitable change from occurring (264). Respondents are anxious, nervous, and afraid about

how the laboratory closures will impact their research careers. By making these unconscious bargains with themselves, they are still trying to negotiate a way for things to return to the way they were prior to COVD-19 (264,288). With depression, respondents are realizing that the change they have been bargaining to avoid, is unavoidable (288). Respondents in this stage are becoming aware that the consequences of missing multiple months of research time will impact them, leaving them discouraged. Both bargaining and depression stages have been documented in the literature as being associated with respondents beginning to come to terms with the new reality post-change (264,288). This is a significant challenge, both cognitively and emotionally, and often results in respondents cycling between these two stages, as well as the anger stage (288). This previously documented pattern is consistent with our data trends from respondents. What is known on how to support persons during these stages aligns with supports previously identified by respondents, listening to the person experiencing grief and then providing empathy and compassion (288–290).

Coping and processing change events takes time. Our data suggests graduate students and postdoctoral fellows are still processing the impacts caused by COVID-19. For many junior researchers, the 2020 COVID-19 laboratory closures will be a turning point in their careers. In the coming months, the support provided by supervisors and administrators will be key in assisting graduate students and postdoctoral fellows to cope and adapt. It is important to note that supervisors and administrators may also be experiencing similar grief and stress responses to the

COVID-19 pandemic. Further research into the shutdown experiences and support needed by those in more senior positions is necessary. As laboratories slowly begin to reopen, a new normal for research will be found. When this stability is established, this will allow for acceptance and hope to start growing again.

Limitations

One limitation of this study was the use of self-reported measures, which can be impacted by social desirability bias (291). We attempted to minimize this by having an anonymous data gathering tool with options to skip questions to have respondents feel secure in giving their answers. This research design choice did lead to approximately a quarter of respondents declining to provide demographic information. This lack of information must be considered when making statements about demographic trends.

We are also reliant on accurate self-reporting, as respondents may provide inaccurate information. Past research supports validity of self-reported demographic information (292). Self-reported data on emotion has been documented to change over time (293). Thus, we launched the study as close to the beginning of laboratory shutdowns in Canada as possible to collect a snapshot of respondent emotions.

Another limitation is our respondents' sample size is relatively small compared to the potential total number of graduate students and postdoctoral fellows in Canada. In 2015, there were over 140,000 graduate students registered at Canadian

Universities (294). Of these, approximately 66,000 were registered in disciplines where laboratory research is a major component (294). There is less data available on the number of postdoctoral fellows in Canada, however, in 2013 there was an estimated 9,000 (273). Thus, our respondent sample represents 0.4% of this total population. This small sample size could lead to population biases in experience, such as most of the respondents were from biology or health research-based backgrounds. The geographic distribution of respondents was concentrated in Ontario and Quebec, however, these trends reflect known concentrations of graduate students across Canada (294). These limitations due to sample size must be considered when making generalization about the Canadian laboratory-based graduate student and postdoctoral fellow population as a whole.

Additionally, the stress and increased responsibilities experienced by our target population may have led to potential respondents self-selecting to be those who have the time to participate in a qualitative research study. When applying our findings to their own unique contexts, readers should consult their graduate students and postdoctoral fellows to ensure the themes identified within this manuscript are reflective of their own experiences.

Conclusion

Overall, we have documented the experiences of Canadian graduate students and postdoctoral fellows conducting laboratory-based research during the COVID-19 research shutdown. We used the Kübler-Ross model as a lens to analyse respondents' grief and emotional response resulting from laboratory closures. We

identified that unclear and inconsistent communication from supervisors and administrators led to a sense of chaos and confusion leading up to laboratory closures. The process of stopping experiments, either with uniform or staggered closures, impacted respondents' emotional response to laboratory closures. Respondents reported experiencing high levels of distress while working from home. Barriers and supports to working at home were also identified. Concerns regarding the impact of laboratory closures on graduate students and postdoctoral fellows were identified, particularly those concerning competitiveness of candidate and availability of future research positions. We compiled a list of supports requested by graduate students and postdoctoral fellows to facilitate their return to the laboratory environment including personal protective equipment and protocols, understanding and empathy, guidance and direction, timeline support, and financial support.

Acknowledgements

The authors would like to thank all individuals who helped share information about the study via social media and email. We would also like to thank all graduate students and postdoctoral fellows who gave their time to complete the survey and/or be interviewed. Without their participation this work would not have been possible. Thank you for letting us share your stories.

The authors state no conflict of interest.

Tables

Table 4.1 Migration patterns of graduate students and postdoctoral fellows during the transition to working from home.

Category	N (%)
Remained in same city as their laboratory	224 (79.2)
Traveled to a city within the same province or territory (Less than 1-hour drive)	26 (9.2)
Traveled to a city within the same province or territory (More than 1-hour drive)	18 (6.4)
Traveled to another province or territory	13 (4.6)
Traveled to another country	2 (0.7)

Table 4.2 Characteristics of working from home experiences by respondents across Canada.

Category	N (%)
Dedicated Home Workspace	
No	52 (20.4)
Yes, Shared Workspace	79 (31.0)
Yes, Individual Workspace	124 (48.6)
Participation in course(s) as part of planned studies prior to shutdown	
No	183 (71.5)
Yes, The course transitioned online during shutdown	63 (21.9)
Yes, The course ended during shutdown	4 (1.3)
Project(s) in the peer review process	
No	164 (64.1)
Yes, recently submitted or with an editor	28 (10.9)
Yes, Sent for peer review	16 (6.3)
Yes, Completing revisions (major or minor)	26 (10.2)
Yes, Submitted revisions	10 (3.9)
Yes, Recently accepted	12 (4.7)

Table 4.3 Descriptions of COVID-19 related activities completed by respondents while working at home. Respondent percentages can be found in Figure 3a.

Number	Activity Description
1	Collecting/donating personal protective equipment or other supplies to local hospitals
2	Sharing accurate information about COVID-19 with family and friends
3	Sharing accurate information about COVID-19 with the general public
4	Volunteering your research skills to support research on COVID-19 (in-person or remote work)
5	Volunteering your research skills to support patient testing efforts for COVID-19
6	Supporting family, friends, or others in quarantine (for example, picking up groceries)
7	Supporting health care professionals (for example, picking up groceries, providing childcare support)

Table 4.4 Descriptions of self-care related activities completed by respondents while working at home. Respondent percentages can be found in Figure 3b.

Number	Activity Description
1	Exercise (indoor or outdoor)
2	Meditation or mindfulness
3	Connecting with family and friends by phone
4	Connecting with family and friends by email, text, or other messaging software
5	Connecting with family and friend by video chat
6	Practicing an old hobby or skill (for example, baking, gardening, music, reading)
7	Developing a new hobby or skill (for example, baking, gardening, music, reading)
8	Attending virtual religious or spiritual services
9	Establishing and maintaining routine

Table 4.5 Descriptions of research related activities completed by respondents while working at home. Respondent percentages can be found in Figure 3c.

Number	Activity Description
1	Virtual laboratory meetings
2	Virtual journal clubs
3	Virtual scientific meetings, conferences, or seminars
4	Virtual Committee Meeting
5	Virtual Comprehensive Examination
6	Virtual Thesis Defense
7	Updating laboratory notebooks
8	Creating strategic plans for future experiments
9	Analysis of data gathered before laboratory closing
10	Preparing applications for awards, conferences, scholarships, etc.
11	Writing thesis chapter(s)
12	Writing draft manuscript(s)
13	Writing review article(s)
14	Writing protocols, SOPs
15	Designing scientific figures
16	Working on written revisions to a paper in peer review
17	Organizing reagents and/or data spreadsheets
18	Reading the literature
19	Completing online training or learning new skills virtually
20	Updating your CV, LinkedIn, ORCID, or similar online platform

Table 4.6 Descriptions of household related activities completed by respondents while working at home. Respondent percentages can be found in Figure 3d.

Number	Activity Description
1	Care and supervision of children
2	Supervising Emergency Remote Learning / Homeschooling of children
3	Care of dependent adults
4	Care of pets
5	Completing necessary excursions to support your household (for example, to obtain groceries or medication)
6	Completing necessary excursions to support others (for example, to obtain groceries or medication for family)
7	Cooking meals for myself
8	Cooking meals for others in my household
9	Domestic cleaning tasks (for example, vacuuming, washing dishes, doing laundry)

Table 4.7 Opinions on household distribution of labour. Total population includes respondents who are non-binary or genderfluid, as well a those who did not disclose their gender. N values and percentage values are given for each row. Significance was determined by a two-sided Fisher's exact test using GraphPad Prism 8. Significance was determined by Fisher's exact test using GraphPad Prism 8 (P=0.1100).

Category	No - Uneven distribution of labour	Yes - Even distribution of labour	Total Respondents
Female Respondents	53 (36.8%)	91 (63.2%)	144
Male Respondents	11 (23.4%)	36 (76.6%)	47
Total Population	75 (33.9%)	146 (66.1%)	221

Table 4.8 Recommended Widespread Laboratory Shutdown Procedure Guidelines.

During the Initial Shutdown Period
● Provide clear communication regarding shutdown decisions to graduate students and postdoctoral fellows ● Ensure communications and decisions are consistent between laboratories, departments, and research institutes at the same institution, where possible ● If major differences in policy are required between research groups due to research contexts, make the reason shutdown procedures differ explicit to graduate students and postdoctoral fellows to minimize confusion ● If possible, minimize sudden changes between policies that are contradictory over short time periods. In certain emerging situations, this may not be possible. In these cases, acknowledge why this decision has been made on short notice. ● Encourage uniform laboratory closures across departments and research institutions. ● In the event staggered closures are necessary to preserve data, be explicit as to why some individuals are continuing to work when others are not. This will minimize the potential for an implied hierarchy between those with perceived ‘high priority’ and ‘low priority’ projects ● Set up remote access to laboratory servers and data for all lab members

● Distribute technology from the laboratory (computers, monitors, hard drives, etc.) when possible for laboratory members to set up their homework spaces ● Remind laboratory members to bring home more personal belongings and resources than they think they should (i.e. plan for a longer shutdown rather than a short one)
While working from home
● Encourage graduate students and postdoctoral fellows to develop and maintain a routine, as well as create a dedicated working space if possible ● Help maintain routine and personal connections through virtual one on one meetings, laboratory meetings, journal clubs, and other social activities ● When connecting with graduate students and postdoctoral fellows, inquire about their emotional and mental wellbeing in addition to progress on work ● Provide information about mental health and financial supports available to students and fellows ● Provide clear updates on changes in policy on returning to the laboratory or other relevant information
Facilitating the return to the laboratory
● Continue to provide information about mental health and financial supports available to students and fellows ● Be empathetic and provide moral support to students and fellows returning to the laboratory.

- Be explicit in understanding the circumstances surrounding the return to the laboratory, including reduced levels of productivity and data production compared to pre-shutdown.
- Consult laboratory members on their circumstances and build flexibility into the return to work plans to account for individual differences (for example, researchers who are responsible childcare, are immunocompromised, international researchers, etc.)
- Have one on one meetings with returning graduate students and postdoctoral fellows to develop a plan to restart their project. Outline specific research goals and outcomes.
- Ensure students and fellows will not be financially penalized for time lost during the laboratory shutdown, such as loss of funding for going overtime
- Have explicit guidelines as to how degree milestones and timelines will be affected by the laboratory shutdown. If changes are made to previously set guidelines before the shutdown, make these changes in consultation with students who will be affected.

Figures

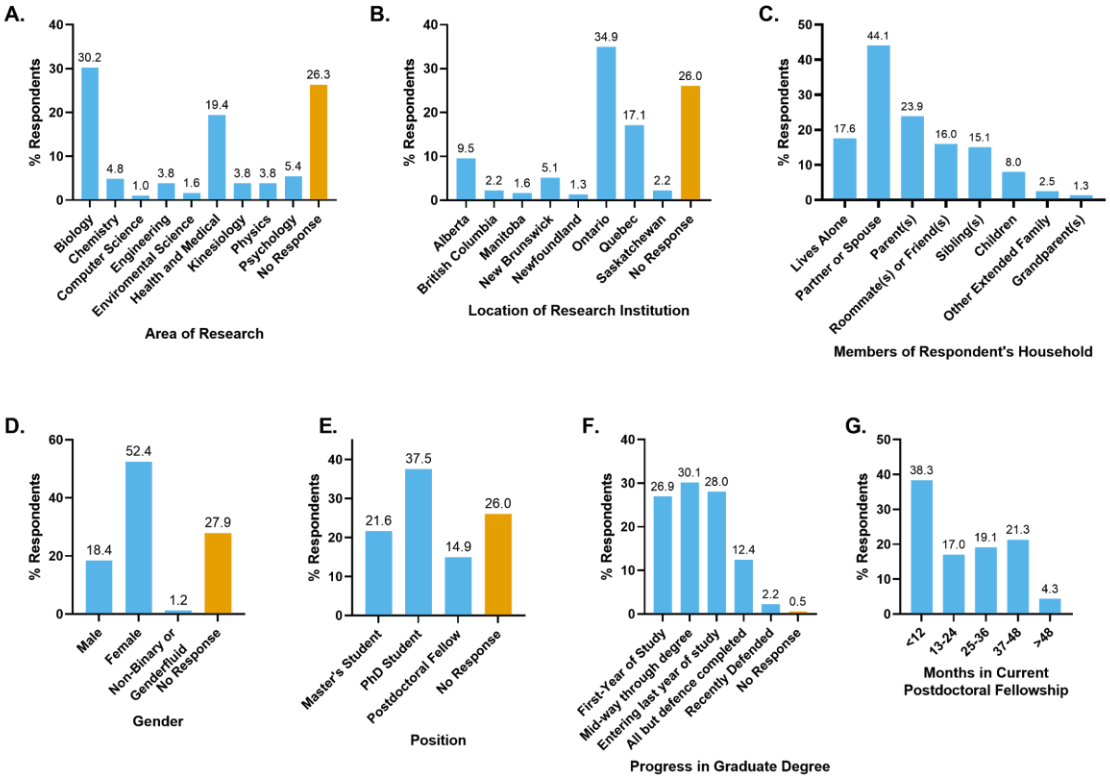

Figure 4.1 Survey Respondent Characteristics. (a) Respondent area of research, N=315. (b) Location of Respondent's research institution, N=315. (c) Living situation of the respondent while working from home. Percentage of respondents with listed members of the household is shown. N= 238. (d) Gender of respondents, N=315. (e) Academic position of respondents, N=315. (f) Progress in graduate degrees for Master's and PhD students. N=186. (g) Months in postdoctoral fellowship position, N=47.

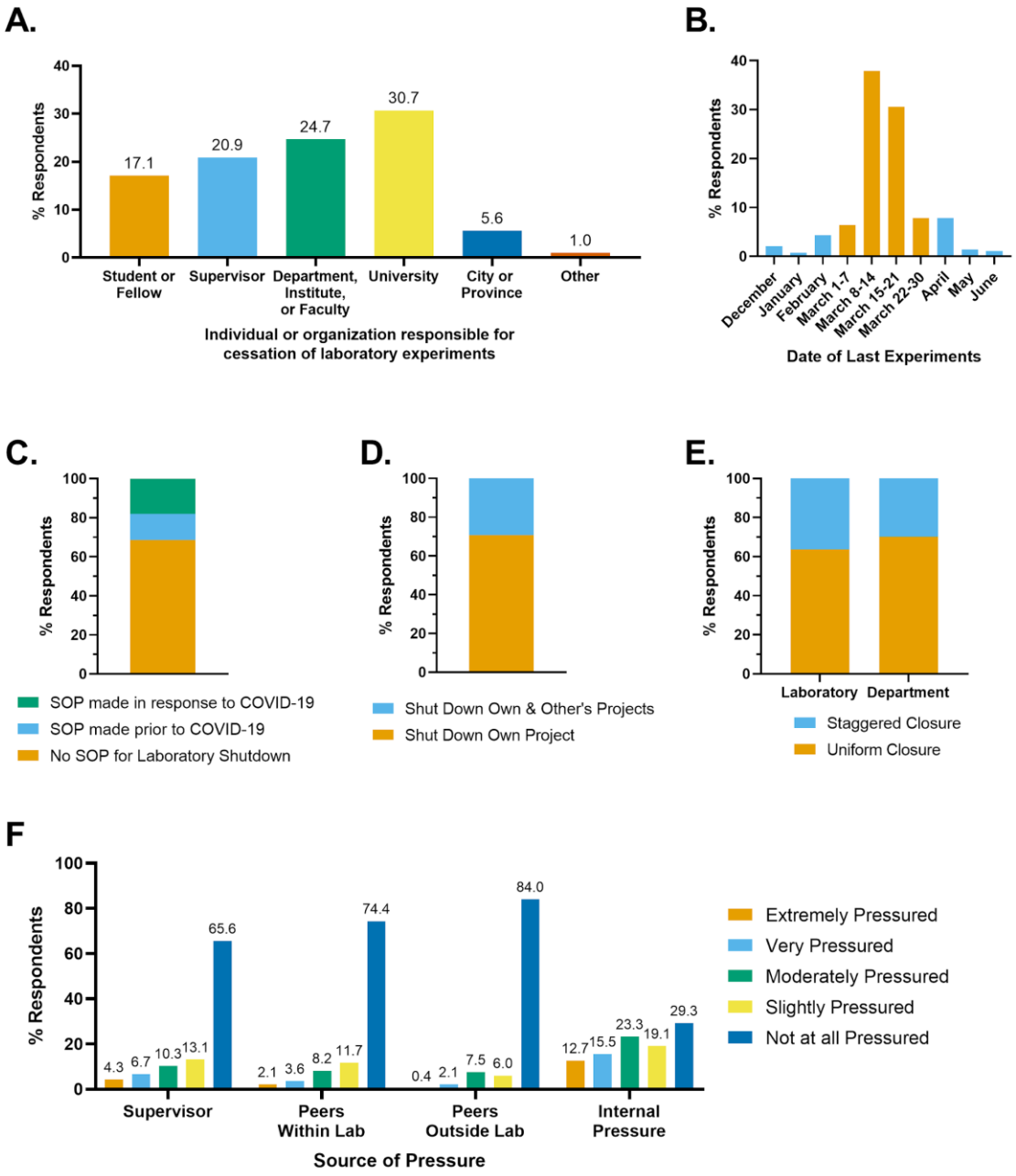

Figure 4.2 Characteristics of laboratory shutdowns experienced by respondents across Canada. (a) Respondent description of the individual or organization, including the respondent themselves, which made the decision to cease laboratory experience. (b) Date of last experiments performed by

respondents. (c) Prevalence of Standard Operating Procedures (SOPs) for fast laboratory closures. (d) Project shutdown responsibilities of respondents. (e) Closure practices of respondent laboratories and departments. Uniform closure describes scenarios where all work stopped at approximately the same time. Staggered closure describes scenarios where some individuals transitioned to work from home while others continued to work in lab. (f) Prevalence of pressure to keep working during laboratory closures.

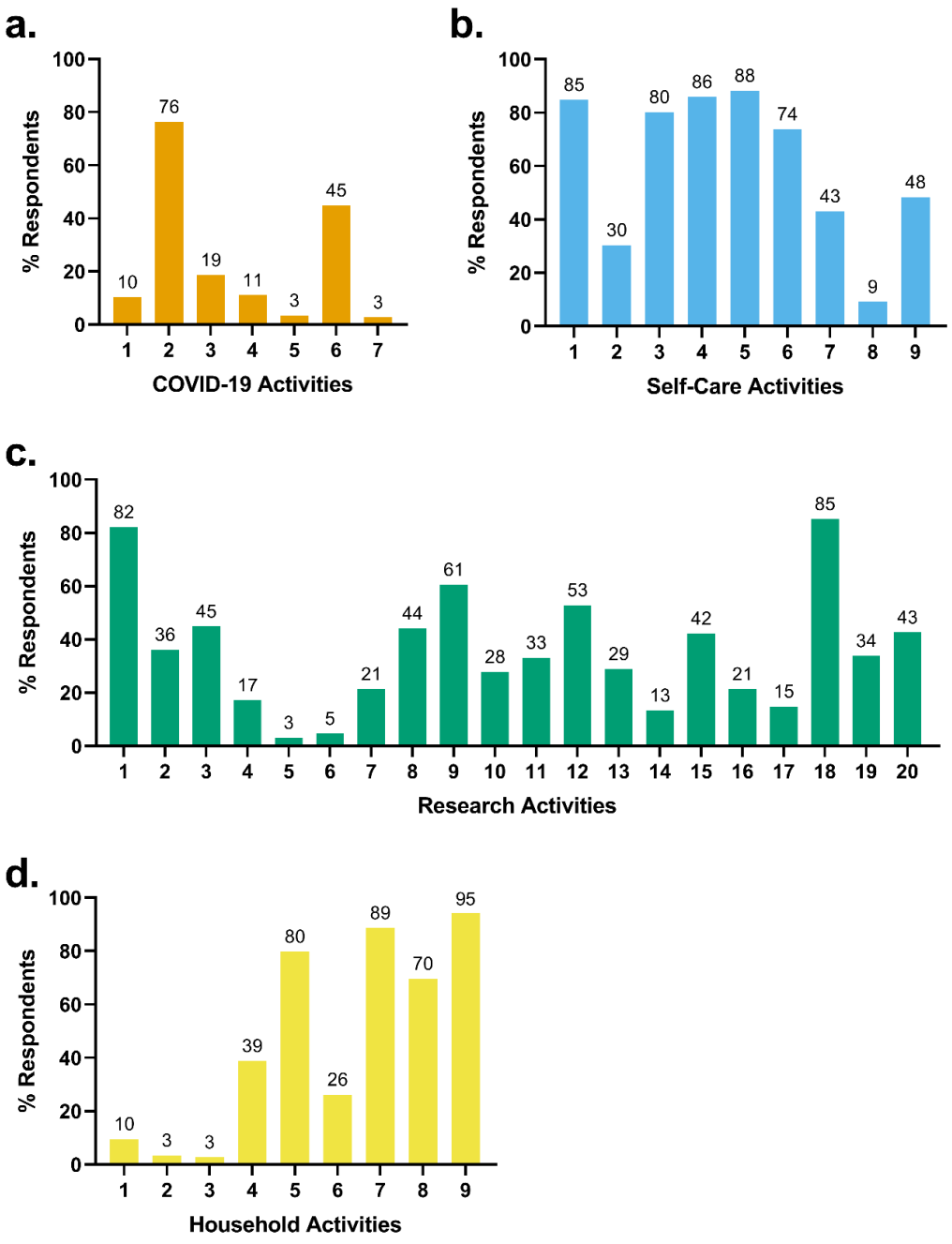

Figure 4.3 Activities conducted by graduate students and postdoctoral fellows while working from home. Values are displayed in percentage of total respondents across (a) COVID-19, (b) Self-Care, (c) Research, and (d) Household related activities. N=263. Full list of activity descriptions available in Tables 3-6.

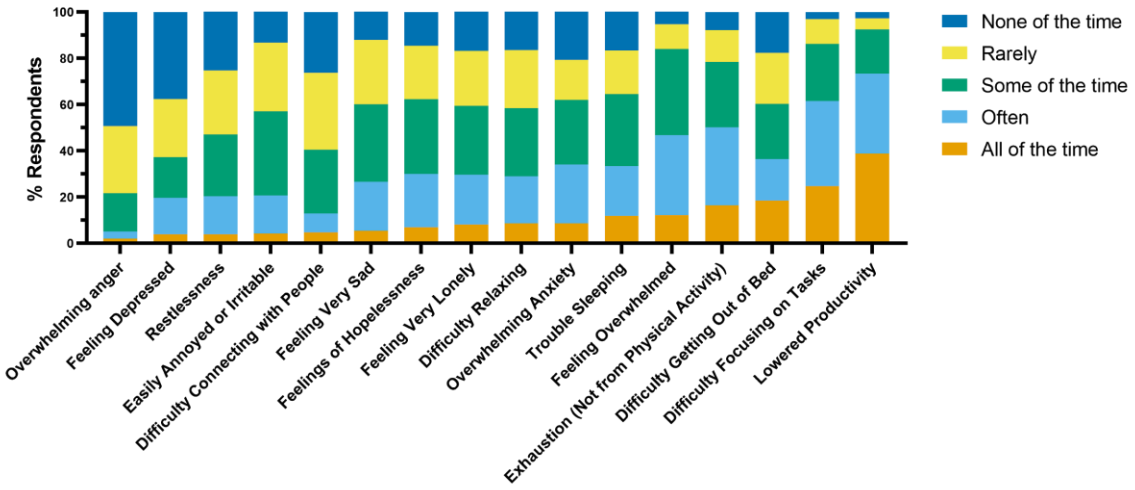

Figure 4.4 Self-reported symptoms of distress while working from home during COVID-19. Values are displayed in percentage of total respondents across 16 symptoms of distress. N=254-256. Items are ranked from lowest to highest percentage of respondents reporting feeling “All of the time”.

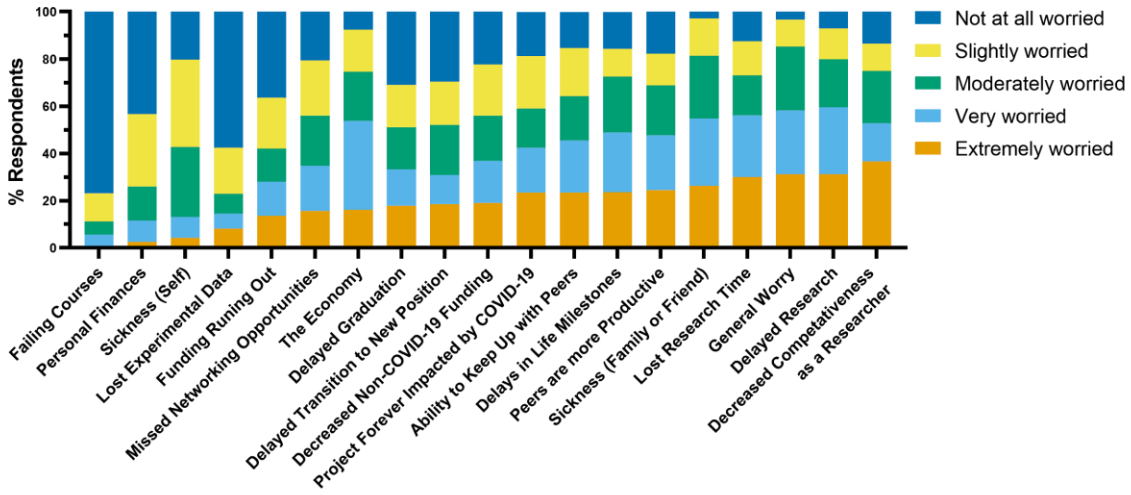

Figure 4.5 Graduate students and postdoctoral fellows' concerns related to the COVID-19 pandemic. Values are displayed in percentage of total respondents across 19 potential areas of concern. N=234-237. Items are ranked from lowest to highest percentage of respondents reporting feeling "Extremely Worried".

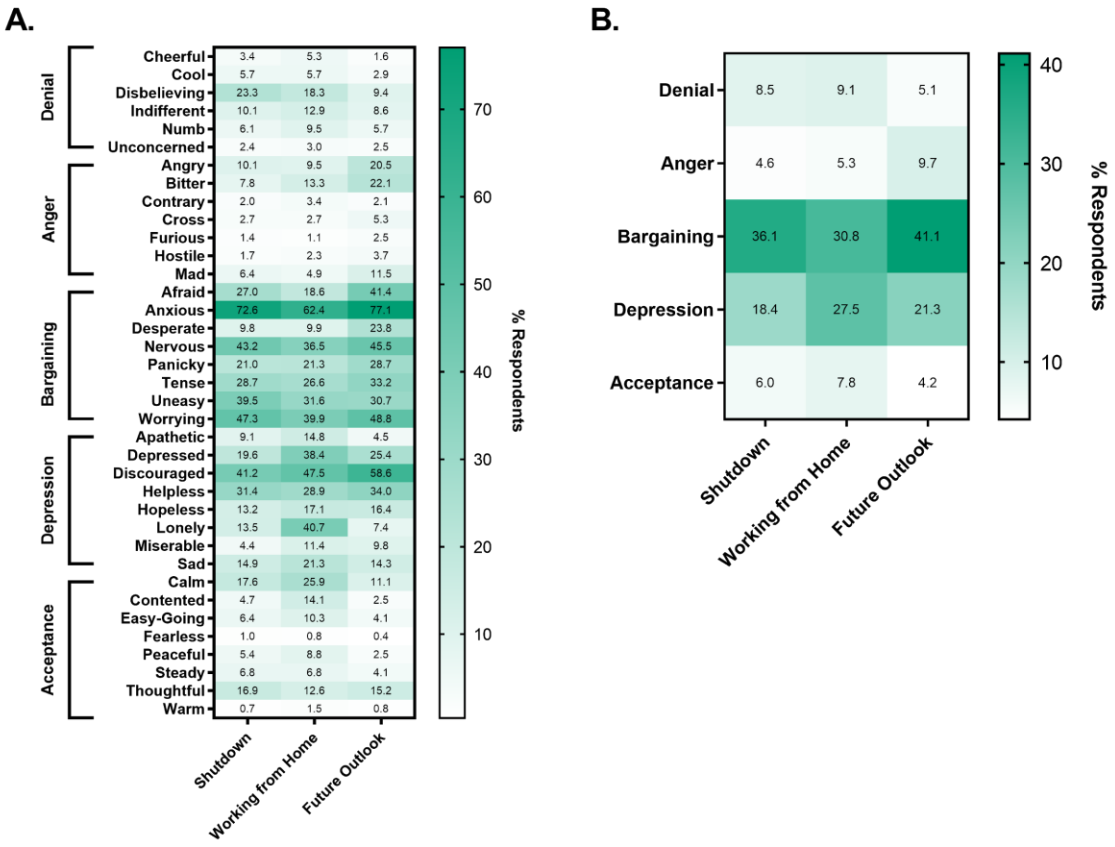

Figure 4.6 Kübler-Ross analysis of emotions experienced by graduate students and postdoctoral fellows across timepoints. Percentage of respondents reporting indicated emotions during laboratory shutdown, while working from home, and when they think of the future. Categorization of emotions by the Kübler-Ross model of grief based on work by Clapper (1991). (a) Full list of emotions experienced during COVID-19. (b) Composite score of overall Kübler-Ross groupings of emotions.

Supplementary Information

All supplementary information is available online.

Supplementary Material 1. Online Survey Protocol.

Supplementary Material 2. Interview Protocol.

Supplementary Table 3. Qualitative codebook and representative quotations.

Supplementary Table 4. Further Survey Respondent Characteristics.

Supplementary Table 5. Interview Respondent Characteristics.

Supplementary Table 6. Participation in shutting down other's experiments, stratified by academic position. N values and percentage values are given for each row. This sample does not include respondents who did not disclose their academic position. Significance was determined by a two-sided Fisher's exact test with Bonferroni correction using GraphPad Prism 8 and R ($P>0.9999$).

Supplementary Table 7. Differences in activities conducted by respondents while working from home, stratified by gender. Significance differences between female and male respondents was determined by Fisher's exact test with Bonferroni correction using GraphPad Prism 8 and R. Total population includes respondents who are non-binary or genderfluid, as well a those who did not disclose their gender.

Supplementary Table 8. Differences in activities conducted by respondents while working from home, stratified by academic position. Significance

differences between graduate student (Masters and PhD students) and postdoctoral fellow (PDF) respondents was determined by Fisher's exact test with Bonferroni correction using GraphPad Prism 8 and R. Total population includes respondents who did not disclose their current academic position.

Supplementary Table 9. Symptoms of distress, stratified by respondent gender. Percentage value represented those who did not respond “None of the time” to the indicated distress item. Significance was determined by two-sided Fisher's exact test with Bonferroni correction using GraphPad Prism 8 and R. Total population includes respondents who are non-binary or genderfluid, as well a those who did not disclose their gender.

Chapter 5: The impact of the COVID-19 pandemic on perceived publication pressure among academic researchers in Canada

The material in this chapter is a reprint of the following publication:

Suart, C., Neuman, K., & Truant, R. (2022). The impact of the COVID-19 pandemic on perceived publication pressure among academic researchers in Canada. *PloS one*, *17*(6), e0269743. doi: 10.1371/journal.pone.0269743

Changes were made in the following publication for continuity and formatting.

Contributions to Publication

CS was first author of this manuscript and contributed 88% of all efforts relating to this project. CS conceptualized the study, designed the methodology, and was the lead author for data curation and formal analysis. KN supported participant recruitment and the analysis process. CS wrote the initial manuscript. KN and RT edited the manuscript. Funding for this work was obtained by RT and CS.

Implications of Work

An increasing number of PhD graduates along with a decreasing number of tenure-track academic positions has resulted in increased competition within academia

(295,296). This has led to an increased emphasis on metrics which may influence the likelihood of obtaining a research position, such as a researcher's number of publications, grants, and citations (258,297). The term "publish-or-perish" has emerged to describe the pressure to publish frequently in high-impact journals experienced by academics (37–39).

In our previous study examined in Chapter 4, we found that 71% of graduate students and postdoctoral fellow respondents felt internal pressure to continue working despite laboratory closure orders due to COVID-19 (298). When prompted for additional detail, respondents shared not being able to submit manuscripts due to lack of data and falling behind due to lost research time, which is consistent with previous studies examining publication pressure (259,298). As such, we sought to build on our previous work to further examine how COVID-19 has impacted publication pressure experienced by academic researchers in Canada. We assessed how COVID-19 has changed perceived publication pressure in Canada using the revised Publication Pressure Questionnaire (259,299). Further, we examine multiple demographic factors including discipline, career stage, gender, disability, and citizenship to identify potential disparities between subpopulations.

We will need to wait to see the full impact of this publication. However, these findings have been discussed at conferences and cited by academics arguing for equity-focused approaches to supporting researchers impacted by COVID-19

Since its publication in June 2022, this manuscript has been cited two times.

The impact of the COVID-19 pandemic on perceived publication pressure among academic researchers in Canada

Celeste Suart[1], Kaitlyn Neuman[1], and Ray Truant[1,*]

1 Department of Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Ontario, Canada

* Corresponding Author

Email: truantr@mcmaster.ca (RT)

Abstract

The phenomenon of “publish-or-perish” in academia, spurred on by limited funding and academic positions, has led to increased competition and pressure on academics to publish. Publication pressure has been linked with multiple negative outcomes, including increased academic misconduct and researcher burnout. COVID-19 has disrupted research worldwide, leading to lost research time and increased anxiety amongst researchers. The objective of this study was to examine how COVID-19 has impacted perceived publication pressure amongst academic researchers in Canada. We used the revised Publication Pressure Questionnaire, in addition to Likert-type questions to discern respondents’ beliefs and concerns about the impact of COVID-19 on academic publishing. We found that publication pressure increased across academic researchers in Canada following the pandemic, with respondents reporting increased stress, increased pessimism, and

decreased access to support related to publishing. Doctoral students reported the highest levels of stress and pessimism, while principal investigators had the most access to publication support. There were no significant differences in publication pressure reported between different research disciplines. Women and non-binary or genderfluid respondents reported higher stress and pessimism than men. We also identified differences in perceived publication pressure based on respondents' publication frequency and other demographic factors, including disability and citizenship status. Overall, we document a snapshot of perceived publication pressure in Canada across researchers of different academic career stages and disciplines. This information can be used to guide the creation of researcher supports, as well as identify groups of researchers who may benefit from targeted resources.

Introduction

Hypercompetition is pervasive within academia (295,296). The growing number of PhD graduates, combined with the shrinking number of academic research positions has led to increased emphasis on quantifying research outputs to differentiate oneself from peers when applying for academic positions or funding (258,300,301). The number of publications, grants, and citations a researcher has can influence the likelihood of obtaining research positions and further funding (297,302–304). This culture of "publish-or-perish" has led to increased pressure on academics to publish research (37–39).

Scholars have pointed to publication pressure as a necessary aspect of academia to incentivize the generation of high-quality research (305,306). This is a long-standing phenomenon within the academy, with the first known use of the phrase “publish-or-perish” in the literature occurring in 1927 (307). However, in the past decade, there has been a shift acknowledging the potential negative impacts of “publish-or-perish”, including decreases in sharing raw data or unpublished findings, decreased academic creativity, less rigorous research, and increased academic misconduct (257,308–314). As perceived pressure to publish has been reported to vary between countries and disciplinary contexts, so to does the prevalence of these outcomes (314,315). Nevertheless, high levels of publication pressure have been associated with increased feelings of burnout and exhaustion (316–318). This challenging relationship between academia at large and the “publish-or-perish” culture has been further complicated by COVID-19.

In spring 2020, the COVID-19 pandemic resulted in unprecedented closures of academic institutes worldwide (319). Research from multiple groups has shown that the pandemic has exacerbated previously identified challenges and harms that academic researchers face, including reduced job security, decreased funding opportunities, and worsening mental health (272,298,320–324). Our work examining the impact of pandemic laboratory closures on Canadian graduate students and postdoctoral fellows reported 70.7% of respondents felt internal pressure to continue working despite shutdown orders (298). This pressure was

attributed to fears of losing research time and not being able to submit manuscripts due to lack of data, aligning with past descriptions of publication pressure (298).

The purpose of this study was to further explore how COVID-19 has impacted perceived publication pressure experienced by academic researchers in Canada. Our past study was restricted to research trainees in laboratory settings, limiting the generalizability of findings to other disciplines and academic positions (298). Thus, we have widened our scope to include graduate students, postdoctoral fellows, and principal investigators of all disciplines at Canadian academic institutions. To do this, we have built off of the work by Haven and colleagues' revised Publication Pressure Questionnaire to quantitatively assess and compare perceived publication pressure across demographic groups (259,299). We aimed to explore how COVID-19 has changed perceived publication pressure in Canada, as well as ascertain disparities in publication pressure between different subpopulations. This would shed light on the Canadian-specific context of publication pressure, as previous literature has often grouped Canadian data with other countries such as the United States and United Kingdom (315). These findings would also help inform the creation of resources and supports for academic research and identify where tailored interventions would be beneficial.

Methods

Ethics approval

This study and consent protocol was approved by the Hamilton Integrated Research Ethics Board (HiREB) under project number 13184 on March 8, 2021. A protocol amendment was approved on April 12, 2021, to allow the investigators to contact participants in a previous study who consented to be contacted by email about additional research to advertise the current study (298). Due to our use of an anonymized online survey, consent to participate was obtained electronically through respondents selecting “Yes, I agree to participate” to access the survey content. Surveys containing incomplete responses were treated as participant withdrawal and not analyzed.

Participants and recruitment

The target population for this study included all academic researchers (master’s students, PhD students, postdoctoral fellows, and principal investigators) at Canadian research institutions. Graduate student (master’s and PhD students) respondents were limited to those enrolled in thesis-based research programs. Graduate students from course-based programs were not eligible to participate. There were no inclusion or exclusion criteria based on research discipline, age, citizenship, disability, gender, or race.

In the Canadian system, postdoctoral fellows are persons with a PhD or PhD-equivalent degree completing additional research and training under the

mentorship of a principal investigator, typically over a period of two to five years, to develop the competencies needed to hold an independent research appointment (325). Principal investigators are individuals with a PhD or PhD-equivalent degree with an appointment to a research institution allowing them to pursue research activities independently and autonomously (326). We use the term 'research institution' to encompass universities, colleges, academic hospitals, and federal institutions in Canada which engage in research activities. Industry, privately-funded, or charity-based research organizations were not included in this study.

The study was advertised online via Twitter, Facebook, and email. Twitter and Facebook advertisements included an overview of the study purpose, recruitment criteria, and a weblink to access the survey. An electronic letter of information was provided at the beginning of the survey instrument prior to obtaining participant consent. Participants contacted by email were provided with the same portable document format letter of information and the survey weblink.

For email advertisements, the investigators contacted academic email list coordinators to request permission to contact their subscribers with information about the study. This included departmental or faculty administrative staff, graduate student associations, postdoctoral fellow associations, faculty associations, professional organizations, and research interest groups. These individuals or organizations were approached due to their ability to share study information widely with academic researchers.

Additionally, the investigator contacted participants from a previous study on the impact of COVID-19 on graduate students and postdoctoral fellows (298) who had given their consent to be emailed about future research studies. These individuals were contacted by email following the same protocols as the email list advertisements. The survey was open from April 5, 2021, to April 30, 2021, with 1020 participants completing all survey sections.

Survey protocol

The survey was delivered through LimeSurvey, taking approximately 5-10 minutes to complete (S1 Appendix). The survey instrument comprised of three sections; demographic questions, the revised Publication Pressure Questionnaire, and Likert-type questions about respondent beliefs related to COVID-19 and academic publishing.

For some questions, we stratified participant responses based on time period. 'Pre-COVID' refers to the period before widespread closures due to the COVID-19 pandemic in March 2020, while 'post-COVID' refers to approximately one year post these initial closures in April 2021. Pre-COVID responses reflect a participants' memory of events prior to the pandemic onset.

The revised Publication Pressure Questionnaire is a validated and reliable survey instrument to measure perceived publication pressure in academic researchers (259). It consists of three subscales each with six items scored on a 5-point Likert scale from "Totally Disagree (1)" to "Totally Agree (5)". The score for each subscale

is calculated by taking the average of the six items within the subscale. Six of the eighteen items across all three subscales are protective factors rather than risk factors. Protective factors would decrease perceived publication pressure, while risk factors would increase perceived publication pressure. Thus, protective factors must be recoded inversely (“Totally Disagree (5)” to “Totally Agree (1)”) before subscale scores are calculated (299). The presence of these inverted items helps ensure the internal consistency of the survey instrument.

The Publication Stress subscale represents the stress associated with feeling compelled to publish research frequently (259). The Publication Attitude subscale reflects a researcher's outlook on publication, be it optimistic or pessimistic (259). The Publication Resources subscale includes factors such as supportive colleagues and academic freedom which can decrease pressure associated with publishing (259).

If someone scores close to 5.00 across all three subscales, that indicates they are experiencing high publication-related stress, have a pessimistic view of publishing, and have limited access to resources. Conversely, a researcher with subscale scores close to 1.00 experiences little publication-related stress, is optimistic about publishing in their field, and has access to multiple supporting resources.

All data collected through the survey was anonymized. Demographic questions; including the location of respondents’ academic institution, gender, race or ethnicity, disability, and citizenship; had options to indicate they would prefer not

to answer. Participants were able to skip all survey questions. However, surveys containing any blank responses were treated as participant withdrawal from the study and were not included in the analysis. After accessing the welcome page, 72.0% of individuals completed the full survey.

Following survey completion, respondents could opt-in to receive information about the results of the study by email, as well as entering a draw for one of ten 25$ GIFTPASS™ gifts certificates from giftcertificates.ca. Following the closure of the survey on April 30, 2021, the emails of respondents wishing to enter the draw were numbered alphabetically. The ten winners were selected using a random number generator and contacted by email.

Analysis

A minimal dataset can be found in S2 Appendix, with some demographic variables omitted for participant confidentiality. Descriptive statistics were generated for demographic and Likert-type scale belief questions. A Likert-type scale is a five-point scale by which respondents can rate how much they disagree or agree with a given statement (327). Mean scores for each Publication Pressure Questionnaire were calculated and stratified across demographic factors. Two-tailed Paired Student's t-tests, independent Student's t-test, and one-way ANOVA analysis were completed where indicated. We corrected for multiple comparisons with Bonferroni correction. When comparing subpopulations stratified by demographic factors, we included datasets which were greater than or equal to 5% of the total sample population. Eta squared values were used to determine effect size, with 0.01

representing a small effect, 0.06 representing a moderate effect, and 0.14 representing a large effect (328). Descriptive statistics and statistical analysis were completed in SPSS Statistics for Windows (IBM Corporation, Armonk, USA), with additional analysis completed using R (Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism 8 (GraphPad Software, San Diego, USA). For all graphs, error bars show mean and standard deviation. The width of the distribution of scatter plot points represents the proportion of values in the dataset at that point.

Results

Respondent sample characteristics

We received 1020 complete responses to the online survey (Table 5.1). Slightly over half of respondents were graduate students (56.5%), with 19.7% being postdoctoral fellows and 23.9% being principal investigators (Table 5.1). Graduate students were stratified by degree level. Principal investigators were stratified by career stage as defined by the Tri-Council of Canadian research funding agencies. Career stage is determined by the number of years after the start of their first independent research appointment; early-career (<5 years), mid-career (5-15 years), and senior (15+ years) (326). When asked about their goal career field following their training, 51% of graduate students and postdoctoral fellows indicated academia as their preferred field, with the remainder indicated a non-academic field (S1 Table).

To identify trends across research disciplines, we stratified respondents using disciplinary domains established by the three Canadian federal research funding agencies: the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council (NSERC), and the Social Sciences and Humanities Research Council (SSHRC). Respondents did not have to actively be receiving funding from CIHR, NSERC, or SSHRC, but only identify which funding agency mandate their research would be aligned with (329). There was a relatively even distribution of respondents across federal funding agencies, with 31.5% from health sciences disciplines, 30.0% from natural sciences and engineering, and 38.5% from social sciences and humanities (Table 5.1).

When asked about their gender identity, 47.5% of respondents were women, 45.3% were men, 1.3% were non-binary or genderfluid, and 6.0% preferred not to disclose (Table 5.1). 15.1% of respondents identified as having a disability (Table 5.1). 80.0% were Canadian citizens or permanent residents (Table 5.1). We had respondents from every province and territory in Canada, though Ontario had the largest representation (43%), followed by British Colombia (16%) and Alberta (8%) (S2 Table). Most respondents identified as white (S3 Table).

We asked respondents to identify whether they published less, similar to, or more frequently than their peers. Pre-COVID responses indicated that 30.7% of respondents thought they published less than their peers, 55.4% thought they published a similar amount, while 13.9% thought they published more frequently (Table 5.2). Post-COVID, the number of respondents estimating that they

published less than their peers increased (40.5%), while those thinking they published similar (47.0%) or more than (12.5%) their peers decreased (Table 5.2).

Publication related pressures increased following the COVID-19 pandemic

When examining our entire respondent population prior to COVID-19, we found academics in Canada scored highest on Publication Attitude (M=3.31), followed by Publication Stress (M=3.20), indicating heightened stress and an overall negative attitude regarding academic publishing (Figure 5.1). The average publication Resources score was lower at 2.78 (Figure 5.1). Compared to past Publication Pressure Questionnaire data from Dutch academics in 2019, our respondents had lower Attitude scores, similar Stress scores, and higher Resources scores (259).

All publication pressure scores increased for the total population post-COVID-19 (Figure 5.1). This includes significant increases in Stress score (M=3.38, $p<0.0001$, eta squared=0.082, paired Student's t-test), Attitude score (M=3.37, $p=0.0011$, eta squared=0.017 paired Student's t-test), and Resources score (M=3.38, $p<0.0001$, eta squared=0.075 paired Student's t-test).

Publication pressure by academic position

Canadian academics at different career stages reported different levels of publication pressure pre- and post-COVID (Figure 5.2, S4 Table, S1 Figure). All subscale scores increased across all academic positions following COVID-19 (S4 Table). Master's degree students had significant increases in Stress ($p=0.00014$, eta squared=0.122, paired Student's t-test) and Resources scores ($p=0.033$, eta

squared=0.65, paired Student's t-test) (S1 Figure A). Doctoral students had significant increases in all subscale scores (Stress $p<0.0001$ eta squared=0.082, Attitude $p=0.0485$ eta squared=0.025, Resources $p<0.0001$ eta squared=0.126, paired Student's t-test) (S1 Figure B). Postdoctoral fellows had significant increases in Stress scores ($p=0.0075$, eta squared=0.067, paired Student's t-test) (S1 Figure C). Mid-career principal investigators had significant increases in Resources score ($p=0.00016$, eta squared=0.280 paired Student's t-test) (S1 Figure E). There were no significant score increases post-COVID reported by early-career and senior principal investigators (S1 Figures D, F).

Other perceived publication pressure trends emerge when comparing different academic positions (Figure 5.2, S4 Table). Before COVID-19, doctoral students had the highest Stress scores (M=3.29), followed by senior principal investigators (M=3.27) (S4 Table). Master's students ($p=0.0041$, one-way ANOVA) and postdoctoral fellows ($p=0.020$, one-way ANOVA) reported significantly lower Stress scores than doctoral students (Figure 5.2A). Mid-career principal investigators reported the highest Attitude scores (M=3.52), followed by doctoral students (M=3.38) (S4 Table). Master's students had significantly lower Attitude scores compared to doctoral students ($p=0.0015$, one-way ANOVA) and mid-career principal investigators ($p=0.0020$, one-way ANOVA), while postdoctoral fellows ($p=0.039$, one-way ANOVA) have significantly lower scores than mid-career principal investigators (Figure 5.2A). Principal investigators of all levels had lower Resource scores than postdoctoral fellows or graduate students, with mid-

career and senior principal investigators having significantly lower scores than graduate students, postdoctoral fellows, and early-career principal investigators (Figure 5.2A). Academic position had a small effect on Stress (partial eta squared=0.019) and Attitude scores (partial eta squared=0.024), and a moderate effect on Resources scores (partial eta squared=0.065) prior to the onset of the COVID-19 pandemic.

There are fewer significant differences in perceived publication pressure between academic positions post-COVID-19 (Figure 5.2B). Postdoctoral fellows have significantly lower Stress scores than doctoral students (p=0.030, one-way ANOVA), while master's students continue to have Attitude scores significantly lower than doctoral students (p=0.001, one-way ANOVA) and mid-career principal investigators (p=0.0072, one-way ANOVA) (Figure 5.2B). Despite post-COVID Resources scores increasing for all career stages, mid-career and senior principal investigators continue to have significantly lower scores than graduate students and postdoctoral fellows, while only senior principal investigators have significantly lower Resources scores than early-career investigators (Figure 5.2B). Post-onset of COVID-19, Academic position had a small effect on all stress scores (Stress partial eta-squared=0.012, Attitude partial eta-squared=0.023, and Resources partial eta-squared=0.054).

Some differences emerge when we stratify graduate student and postdoctoral fellow perceived publication pressure scores by their goal career field (S5 Table). Before the COVID-19 pandemic, research trainees with the goal career field of

academic had higher Stress (M=3.28, p=0.00004, one-way ANOVA) and Attitude scores (M=3.36, p=0.0063, one-way ANOVA) than trainees hoping to enter non-academic fields that value publication (Stress M=3.05, Attitude M=3.21) (S5 Table). However, trainees hoping to enter academia had significantly lower Resources scores (M=2.79) than trainees hoping to enter non-academic fields which value publication (M=2.78, p=0.0081, one-way ANOVA) and which do not consider publication history (M=2.95, p=0.0003, one-way ANOVA) (S5 Table). Goal career field had a small effect on all three publication pressure scales prior to COVID-19 (partial eta squared =0.012-0.025).

While all mean perceived publication pressure subscale scores increased following COVID-19, similar variations between trainees with different career goals continue (S5 Table). Trainees aiming to enter academia have significantly higher Stress (M=3.51, p<0.0001, one-way ANOVA) and Attitude scores (M=3.44, p=0.00043, one-way ANOVA) than their peers wanting to enter non-academic fields that value publication (Stress M=3.20, Attitude M=3.24) (S5 Table). Trainees who were wanting to enter non-academic fields that do not consider publication history had significantly higher Resource scores (M=3.09) compared to non-academic fields which value publications (M=2.82, p=0.029, one-way ANOVA) and academia (M=2.79, p=0.00058, one-way ANOVA) (S5 Table). After the onset of the pandemic, goal career field continued to have a small effect on the publication pressure scales (partial eta squared=0.019-0.036).

Publication pressure by research funding agency

When scores are stratified by the federal research funding agency of respondents, all perceived publication stress scores increased following COVID-19 (S6 Table). However, only the increases in Stress and Resources scores were significant ($p<0.0001$, paired Student's t-test) for all three research funding agencies (Figure 5.3). Research agency affiliation had a moderate effect on Stress scores (CIHR eta squared=0.082, NSERC eta squared=0.091, SSHRC eta squared=0.074) and Resources scores (CIHR eta squared=0.086, NSERC eta squared=0.075, SSHRC eta squared=0.067). Interestingly, there were no significant differences in any perceived publication stress subscale scores between CIHR, NSERC, and SSHRC respondents before or after the COVID-19 pandemic (S2 Figure). These findings suggest that academic discipline did not impact pressure to publish experienced by Canadian academics, which differs from past data suggesting that researchers in the humanities perceive greater publication stress (259).

Publication pressure by gender

Next, we examined differences in perceived publication pressure when respondents were stratified by gender identity (Table 5.3). Female respondents (n=484) had significant increases in Stress ($p<0.0001$, eta squared=0.112, paired Student's t-test), Attitude ($p=0.0003$, eta squared=0.041 paired Student's t-test), and Resources ($p<0.0001$, eta squared=0.090, paired Student's t-test) subscale scores following COVID-19 (Figure 5.4A). Male respondents (n=462) had significant increases in Stress ($p=0.0003$, eta squared=0.054, paired Student's t-

test) and Resources ($p<0.0001$, eta squared=0.048, paired Student's t-test) subscale scores following COVID-19, however, the increases in Attitude score were non-significant (Figure 5.4B). All subscale score increases from non-binary or genderfluid respondents were non-significant (Figure 5.4C), which may be in part due to the small sample size (n=13). As there were disparities in sample sizes between different genders, further statistical analysis examining differences in perceived publication pressure between populations focused on female and male respondent scores.

Prior to the COVID-19 pandemic, female respondents reported higher Stress ($M=3.39$, $p<0.0001$, eta squared=0.072, independent Student's t-test) and Attitude scores ($M=3.47$, $p<0.0001$, eta squared=0.065, paired Student's t-test) than male respondents (Stress $M=3.00$, Attitude $M=3.13$) (Figure 5.4D). However, male respondents had significantly higher Resources scores ($M=2.73$, $p=0.0012$, eta squared=0.015, independent Student's t-test) than female respondents ($M=2.58$) (Figure 5.4D). Significant differences in Stress and Attitude scores between female and male respondents remained and increased following the COVID-19 pandemic ($p<0.0001$, independent Student's t-test) (Figure 5.4E). The effect size of gender on Stress (eta squared=0.095) and Attitude scores (eta squared=0.077) increased following the onset of COVID-19. Differences in Resources scores between female ($M=2.72$) and male ($M=2.81$) respondents decreased following the COVID-19 pandemic until there were no longer significant differences between these groups (Figure 5.4E).

Publication pressure by publication frequency

Using respondents' self-identified publication frequency (Table 5.2), we stratified their perceived publication pressure scores before and after the beginning of the COVID-19 pandemic (Tables 5.4, 5.5). Prior to the pandemic, respondents who identify publishing less frequently reported higher Stress scores (M=3.37) than those who published more (M=3.05, $p<0.0001$, one-way ANOVA) or a similar amount to their peers (M=3.14, $p<0.0001$, one-way ANOVA) (Table 5.4). A similar trend emerged with Resources scores, with those publishing less frequently (M=2.80) having significantly higher scores than similar (M=2.57, $p<0.0001$, one-way ANOVA) or more frequently publishing respondents (M=2.34, $p=0.0075$, one-way ANOVA) (Table 5.4). Those publishing at a similar frequency to peers also reported significantly higher Resources scores than those publishing more frequently ($p<0.0001$, one-way ANOVA) (Table 5.4). Publishing frequency had a greater effect size on Resources scores (partial eta squared=0.080) compared to Stress scores (partial eta squared=0.026). There were no significant differences in attitude scores between publication frequency groups (Table 5.4).

Comparable trends in perceived publication pressure continue following the COVID-19 pandemic (Table 5.5). Respondents publishing less frequently (M=3.66) continue to report significantly higher Stress scores than those publishing similarly to (M=3.18, $p<0.0001$, one-way ANOVA) or more than peers (M=3.20, $p<0.0001$, one-way ANOVA) (Table 5.5). Researchers who published less frequently had significantly higher Attitude scores (M=3.52) than respondents who published more

frequently (M=3.38, p<0.0001, one-way ANOVA) (Table 5.5). Trends in Resources scores from before the pandemic continue, with respondents publishing less (M=2.87) having significantly higher scores than similarly to (M=2.76, p<0.0001, one-way ANOVA) and more frequently (M=2.52, p=0.045, one-way ANOVA) than peers (Table 5.5). Respondents who identified as publishing a similar amount to their peers also continued to report significantly higher Resources scores than those publishing more frequently (p=0.00016, one-way ANOVA) (Table 5.5). Unlike publication frequency prior to COVID-19, post-pandemic onset publication frequency had a moderate effect on Stress score (partial eta squared=0.081), compared to small effects on Attitude scores (partial eta squared=0.037) and Resources scores (partial eta squared=0.030).

Publication pressure by other demographic factors

Fifteen percent of respondents identified as having a disability (Figure 5.1D). There were no significant differences in Stress and Attitude subscale scores before or after the COVID-19 pandemic between respondents with and without a disability (Table 5.6). However, respondents with disabilities had significantly higher Resources scores pre-COVID (M=2.80, p=0.0044, eta squared=0.012, independent Student's t-test), although this difference decreased post-COVID until it was no longer significant (Table 5.6).

Eighteen percent of respondents identified as being a foreign national in Canada (Figure 5.1E). There were significant differences between foreign nationals and Canadian citizens or permanent residents in all perceived publication pressure

subscale scores, both before and after the COVID-19 pandemic (Table 5.7). Foreign nationals reported significantly lower Stress scores both pre-COVID (M=3.03, p=0.00024, eta squared=0.017, independent Student's t-test) and post-COVID (M=3.21, p=0.0040, eta squared=0.012, independent Student's t-test) (Table 5.7). Foreign nationals also had significantly lower Attitude scores pre-COVID (M=3.20, p=0.033, eta squared=0.008, independent Student's t-test), however, there were no significant differences in Attitude scores following the pandemic (Table 5.7). Nonetheless, foreign nationals reported significantly higher Resources scores than Canadian citizens or permanent residents both pre-COVID (M=2.82, p<0.0001, eta squared=0.023, independent Student's t-test) and post-COVID (M=2.93, p<0.0001, eta squared=0.020, independent Student's t-test) (Table 5.7).

When stratifying perceived publication pressure subscale scores by respondent location, we identified several significant differences between respondents in Ontario and other provinces and territories (S7 Table). Respondents in Ontario had significantly higher Stress and Attitude scores than other provinces and territories, both before and after the COVID-19 pandemic (S7 Table). The effect size of location on Stress and Attitude scores increased from small to moderate following the onset of the pandemic (S7 Table). Before the COVID-19 pandemic, location had a moderate effect on Resources scores, with respondents in Ontario had significantly lower Resources scores than multiple provinces and territories (S7 Table). These differences were no longer reported post-COVID (S7 Table). We did

not identify significant differences between populations when stratifying perceived publication pressure subscale scores by respondent ethnicity using categories adapted from the 2016 Statistics Canada Visible Minority and Population Group Reference Guide (S8 Table) (330).

Respondent beliefs and concerns surrounding COVID-19

Following the Publication Pressure Questionnaire, we asked respondents about their beliefs, feelings, and concerns related to academic publishing and the COVID-19 pandemic (Figure 5.5). When asked about their beliefs on how COVID-19 has impacted research within their disciplines, 43.8% agreed or strongly agreed that the pandemic had increased the pressure to publish (Figure 5.5A). This is compared to 20.4% of respondents who disagreed or strongly disagreed that COVID-19 had increased pressure to publish (Figure 5.5A). 68.6% of respondents agreed or strongly agreed that COVID-19 had increased the time needed to conduct research, while 72.9% agreed or strongly agreed that the pandemic had made the process of conducting research more challenging (Figure 5.5A).

Next, we asked about respondents' feelings of being supported while conducting research during COVID-19. Over half of respondents (55.5%) agreed or strongly agreed that they felt supported by peers and colleagues (Figure 5.5B). Fewer respondents agreed or strongly agreed that they felt supported by their department or faculty (47.5%), their academic institution (38.4%), or their research funding agency (35.5%) (Figure 5.5B).

Lastly, we asked respondents about concerns they may have about how their publication frequency during the pandemic will affect them going forward. Respondents agreed or strongly agreed that they are concerned their publication frequency during COVID-19 will decrease their competitiveness for future funding opportunities (58.1%) and future academic positions, including tenure (55.0%) (Figure 5.5C).

Discussion

In this study, we assessed the self-reported perceived publication experienced by Canadian academic researchers before and after the COVID-19 pandemic using the revised Publication Pressure Questionnaire (299). We additionally asked respondents about their beliefs on the impact of the pandemic on publishing, the supports they experienced while conducting research during the pandemic, and their concerns about the long-term implications of COVID-19. We know from past literature that there is significant pressure to publish in academia (38,39,257–259). Emerging studies on the effects of the pandemic on academics are showing increased stress levels across all career levels (298,320,321). This aligns with our findings, as publication Stress, Attitude, and Resources subscale scores increased across our total respondent population (S4 Table). Our study captures a snapshot of perceived publication pressure within a Canadian population and allows for quantitative comparisons between demographic groups, as well as other academic populations who have used the revised Publication Pressure Questionnaire.

Overall, these findings point to where similarities and disparities in publication pressure exists between differing population. One unifying factor from this data was the lack of significant difference in perceived publication pressure reported by respondents from different funding agencies (S6 Table, S2 Fig). Unlike Haven and colleagues' analysis of Dutch academics, we did not observe any significant difference between respondents from different research disciplines (259). This suggests that publication pressure is felt equally across research disciplines in Canada, both pre- and post-COVID-19.

On par with the Dutch study, we identified differences in perceived publication pressure between respondents from different academic positions (259). For example, we found that principal investigators tended to have lower Resources compared to postdoctoral fellows and graduate students (Figure 5.2). As principal investigators tend to have more academic freedom, while research trainees are more dependent on others regarding research choices, which might contribute to this difference.

Several differences emerged when we stratified our respondents by gender (Table 5.3, Figure 5.4). Women and non-binary or genderfluid respondents reported higher Stress and Attitude scores than men, both before and after the COVID-19 pandemic (Figure 5.4). This mirrors findings from other groups documenting lower rates of manuscript submissions and publications from female academics during COVID-19 (320,331,332). These challenges have primarily been attributed to unbalanced childcare responsibilities and academic service activities (320,331–

336). Both men and women experienced significant increases in household responsibilities following COVID-19, however, women reported significantly larger increases than men (333).

We also identified differences in publication stress scores between trainees with different career goals (S5 Table). Trainees aiming to enter academia reported higher Stress scores than those wanting to enter non-academic fields, both before and after the pandemic. One potential explanation for this difference in stress is the importance of early career publications for obtaining funding and securing academic research positions. Additionally, trainees aiming to enter academia also had significantly lower Resources scores than peers hoping to enter non-academic fields, implying greater access to supports. Lack of resources and supervisor support has previously been identified as contributors to graduate student attrition (337,338). This trend of Resources scores differences continues when we stratify respondents by their self-rated publication frequency compared to peers (Tables 5.4,5.5). Respondents who publish less frequently have higher Stress and Resources scores than those who report publishing similar amounts or more frequently than their peers. This trend is consistent even after the mean score increases following COVID-19. This variance in Resources scores points to a need for future inquiry of how access to supports influences publication potential and academic career paths.

Differences in Resources scores were also identified when examining other demographic factors such as disability (Table 5.6), citizenship (Table 5.7), and

location (S7 Table). Respondents with disabilities reported significantly higher Resources scores before COVID-19 compared to those without disabilities (Table 5.6). This is consistent with past literature showing researchers with disabilities have lower grant success rates and experience ongoing barriers when conducting academic research (335,339–341). This disparity was no longer present following the onset of COVID-19, due to Resources scores of researchers without disabilities increasing (Table 5.6). Although Stress and Attitude scores from foreign nationals indicate they are less stressed and more optimistic about publishing in Canada, they also had significantly higher Resources scores compared to than their Canadian or permanent resident counterparts (Table 5.7). Respondents from Ontario tended to report significantly higher Stress and Attitude scores then elsewhere in Canada, while simultaneously reporting lower Resources scores (S7 Table). As Ontario receives a greater proportion of research funding and support through federal programs compared to other provinces and territories, this could example the differences in Resources scores (342,343). These differences in perceived publication pressure between demographic groups point to the importance of context and tailoring of research supports to align with community needs.

We did not identify any statistically significant differences in perceived publication pressure when stratifying responses by respondent ethnicity, though this could be attributed to the ethnic homogeneity of our respondent sample. 72.3% of respondents identified as white, which is consistent with past surveys of Canadian

researchers (272,273,344). Other groups have identified strategies to support Black, Indigenous, and other underrepresented minority scholars within the academy during COVID-19, acknowledging the barriers stemming from systematic racism and the disproportionately negative impact of COVID-19 (345–348). Administrators should draw on the findings of such studies when designing resources to support Black, Indigenous, and other underrepresented minority researchers.

The quantitative findings of the revised Publication Pressure Questionnaire reflect respondent beliefs and concerns about the impact of COVID-19 on academic publishing. Just under half of the respondents believed that the pandemic had increased the pressure to publish, while the majority agreed it increases the time and difficulty to complete research (Figure 5.5A). Half of the respondents were also concerned about how their publishing, or lack of publishing, would decrease their competitiveness for funding opportunities and academic positions (Figure 5.5C). This aligns with past research connecting pressure to publish with pressure to obtain grants and long-term career prospects (349). Keeping these perceptions in mind will be important to funding agencies and institutions designing resources and programs to support researchers to recover from the pandemic.

Study limitations

A limitation of our study was the use of the self-reported survey format. Although the best fit for the phenomena we were observing, pressure to publish perceived by individual researchers, such answers can be impacted by social desirability bias

(291,350). We used indirect methods to reduce the potential impact, including using an anonymous online survey, giving options to decline answering demographic questions, and emphasizing respondent confidentiality (350). This data collection method relies on accurate self-reporting, as inaccurate information would skew data and subsequent results. Previous research on the accuracy of self-reported demographic information shows concordance between online self-reported demographic information when compared with other records (292,351) Additionally, we asked respondents to retrospectively assess their perceived publication pressure feelings before the pandemic, which may introduce memory-related biases. Past research involving participants recalling emotions has shown these perceptions can change over time, however, there are mixed reports of whether recalled distress becomes over- or under-estimated with hindsight (293,352–354). Ideally, we would have been able to measure perceived publication pressure experienced by Canadian academics before the pandemic, then compare those numbers with responses from the same participants post-pandemic. This was not possible due to the sudden and unexpected onset of COVID-19.

Another limitation of our study is our sample size (N=1020). There is a lack of accurate, up-to-date statistics available on the total number of graduate students, postdoctoral fellows, and principal investigators in Canada. However, combining data on graduate students registered in research-intensive programs at Canadian universities in 2015 (294), estimates of postdoctoral fellows in Canada in 2013 (273), and data on principal investigators from 2019 (344), we can roughly estimate

approximately 126,000 individuals across Canada meet our eligibility criteria. Our respondent sample would represent 0.8% of eligible participants. Our sample does align with past demographic trends observed in Canadian academic cohorts where such data exists (273,294,344). However, these sample size limitations must be considered when making generalizations.

Another drawback connected to sample size was our small number of non-binary and genderfluid respondents, which limited the statistical conclusions we can draw for this population. This absence of data from gender diverse respondents is not a challenge unique to COVID-19 related research, but an ongoing issue where research studies do not provide options for gender identity outside of male and female (355,356). This points to a need for further exploration of the experiences of non-binary and genderfluid academic researchers, including feelings of publication pressure.

Due to the documented stress and increased responsibilities our target population is experiencing due to the pandemic (298), this may have led to a self-selection bias where respondents experiencing high stress might not have had the capacity to complete the survey. We attempted to minimize this potential self-selection by minimizing the length of time needed to complete our survey instrument. Additional self-select bias may have resulted from our use of a gift card draw to increase survey response and completion rates (357).

Lastly, as the revised Publication Pressure Questionnaire is a relatively new survey tool (259), it is difficult to draw conclusions about absolute levels of publication pressure we observe within our cohort due to the lack of reference populations. Further research in other academic research populations is needed to improve comparisons between countries and other contexts.

Conclusions

Altogether, we documented publication pressure perceived by Canadian academics across multiple disciplines and career stages. Although pressure was perceived equally across research disciplines, we identified differences in publication pressure between academic positions, genders, publication frequency, and other demographic factors. We also recorded an increase in pressure to publish following the COVID-19 pandemic. The “publish-or-perish” phenomenon is not a new concept, but our evidence points to pre-existing stressors, such as competitiveness for funding and academic positions, and pressure to publish being amplified by the pandemic. As pressure increases were different between various demographic groups, administrators at all levels should open a conversation with their affiliated researchers to assess how they are doing and what supports best fit their distinct research context.

Additional research is needed using the revised Publication Pressure Questionnaire to identify differences and similarities between different countries, to identify how funding structures and other contextual factors influence publication pressure. More qualitative research on the experiences of Canadian academics is

needed to identify potential sources for the disparities in perceived publication pressure. Overall, our findings should serve as a jumping-off point for discussion of short-term and structural changes which can be made to encourage a healthy publication culture.

Acknowledgements

The authors would like to thank all participants who responded to our survey, as well as all individuals who helped share information about our study via social media and email. Without your responses, this work would not have been possible. Additionally, the authors would like to thank M. Ogrodnik and M. Suttie who provided feedback on early versions of the survey text.

Tables

Table 5.1 Survey Respondent Characteristics. N= 1020.

Characteristic	**N (%)**
Academic Position of Respondents	
Graduate Student: Master's Degree	166 (16.3%)
Graduate Student: Doctoral Degree	410 (40.2%)
Postdoctoral Fellow	201 (19.7%)
Principal Investigator: Early Career	121 (11.9%)
Principal Investigator: Mid-Career	66 (6.5%)
Principal Investigator: Senior	56 (5.5%)
Research Funding Agency of Respondents	
Canadian Institutes of Health Research (CIHR)	321 (31.5%)
Natural Sciences and Engineering Research Council (NSERC)	306 (30.0%)
Social Sciences and Humanities Research Council (SSHRC)	393 (38.5%)
Gender	
Female	484 (47.5%)
Male	462 (45.3%)
Non-Binary or Genderfluid	13 (1.3%)

Prefer not to Answer	61 (6.0%)
Disability Status	
Identifies as having a disability	154 (15.1%)
Does not identify as having a disability	833 (81.7%)
Prefer not to Answer	33 (3.2%)
Citizenship Status	
Canadian Citizen or Permanent Resident	816 (80.0%)
Foreign National in Canada	187 (18.3%)
Prefer not to Answer	17 (1.7%)

Table 5.2 Respondent Self-identified publication frequency. N=1020.

Publication Frequency	**Pre-Pandemic Onset N (%)**	**Post-Pandemic Onset N (%)**
Less than Peers	313 (30.7%)	413 (40.5%)
Similar to Peers	565 (55.4%)	479 (47.0%)
More than Peers	142 (13.9%)	128 (12.5%)

Table 5.3 Publication Pressure Questionnaire Subscale Scores stratified by gender.

Gender	N	Stress		Attitude		Resources	
		Pre-COVID	Post-COVID	Pre-COVID	Post-COVID	Pre-COVID	Post-COVID
Female	484	3.39 (0.76)	3.63 (0.86)	3.47 (0.68)	3.56 (0.74)	2.58 (0.69)	2.72 (0.66)
Male	462	3.00 (0.62)	3.12 (0.69)	3.13 (0.59)	3.16 (0.64)	2.73 (0.56)	2.81 (0.55)
Non-Binary or Genderfluid	13	3.58 (0.88)	3.78 (0.80)	3.72 (0.64)	3.83 (0.74)	2.42 (0.71)	2.69 (0.93)
Prefer not to Answer	61	3.08 (0.67)	3.22 (0.67)	3.25 (0.69)	3.22 (0.69)	2.76 (0.52)	2.96 (0.57)
Total Population	1020	3.20 (0.72)	3.38 (0.82)	3.31 (0.66)	3.37 (0.72)	2.65 (0.62)	2.78 (0.63)

Values represent mean score with standard deviation in brackets.

Table 5.4 Pre-COVID Publication Pressure Questionnaire Subscale Scores stratified by self-identified publication frequency.

Publication Frequency	**N**	**Stress**	**Attitude**	**Resources**
Less than Peers	313	3.37 (0.74)	3.35 (0.69)	2.80 (0.56)
Similar to Peers	565	3.14 (0.68)	3.26 (0.62)	2.67 (0.59)
More than Peers	142	3.05 (0.79)	3.39 (0.74)	2.24 (0.65)
Total Population	1020	3.20 (0.72)	3.31 (0.66)	2.65 (0.62)

Values represent mean score with standard deviation in brackets.

Table 5.5 Post-COVID Publication Pressure Questionnaire Subscale Scores stratified by self-identified publication frequency.

Publication Frequency	**N**	**Stress**	**Attitude**	**Resources**
Less than Peers	413	3.66 (0.84)	3.52 (0.73)	2.87 (0.62)
Similar to Peers	479	3.18 (0.71)	3.22 (0.68)	2.76 (0.59)
More than Peers	128	3.20 (0.84)	3.38 (0.72)	2.52 (0.71)
Total Population	1020	3.20 (0.72)	3.31 (0.66)	2.65 (0.62)

Values represent mean score with standard deviation in brackets.

Table 5.6 Publication Pressure Questionnaire Subscale Scores stratified by disability identification.

Disability Identification	**N**	**Stress**		**Attitude**		**Resources**	
		Pre-COVID	**Post-COVID**	**Pre-COVID**	**Post-COVID**	**Pre-COVID**	**Post-COVID**
Identifies as having a disability	154	3.14 (0.63)	3.30 (0.76)	3.24 (0.64)	3.34 (0.66)	2.80 (0.64)	2.86 (0.64)
Does not identify as having a disability	833	3.18 (0.72)	3.37 (0.81)	3.30 (0.66)	3.35 (0.73)	2.62 (0.61)	2.75 (0.2)
Prefer not to Answer	33	3.77 (0.88)	3.90 (0.91)	3.74 (0.59)	3.78 (0.66)	2.77 (0.63)	3.03 (0.71)
Total Population	1020	3.20 (0.72)	3.38 (0.82)	3.31 (0.66)	3.37 (0.72)	2.65 (0.62)	2.78 (0.63)

Values represent mean score with standard deviation in brackets.

Table 5.7 Publication Pressure Questionnaire Subscale Scores stratified by citizenship.

Academic Position	**N**	**Stress**		**Attitude**		**Resources**	
		Pre-COVID	**Post-COVID**	**Pre-COVID**	**Post-COVID**	**Pre-COVID**	**Post-COVID**
Canadian Citizen or Permanent Resident	816	3.24 (0.75)	3.42 (0.84)	3.33 (0.67)	3.39 (0.73)	2.61 (0.63)	2.73 (0.65)
Foreign National in Canada	187	3.03 (0.57)	3.21 (0.70)	3.20 (0.59)	3.25 (0.65)	2.82 (0.54)	2.93 (0.52)
Prefer not to Answer	17	3.04 (0.71)	3.16 (0.79)	3.28 (0.91)	3.31 (0.96)	2.99 (0.52)	3.11 (0.41)
Total Population	1020	3.20 (0.72)	3.38 (0.82)	3.31 (0.66)	3.37 (0.72)	2.65 (0.62)	2.78 (0.63)

Values represent mean score with standard deviation in brackets.

Figures

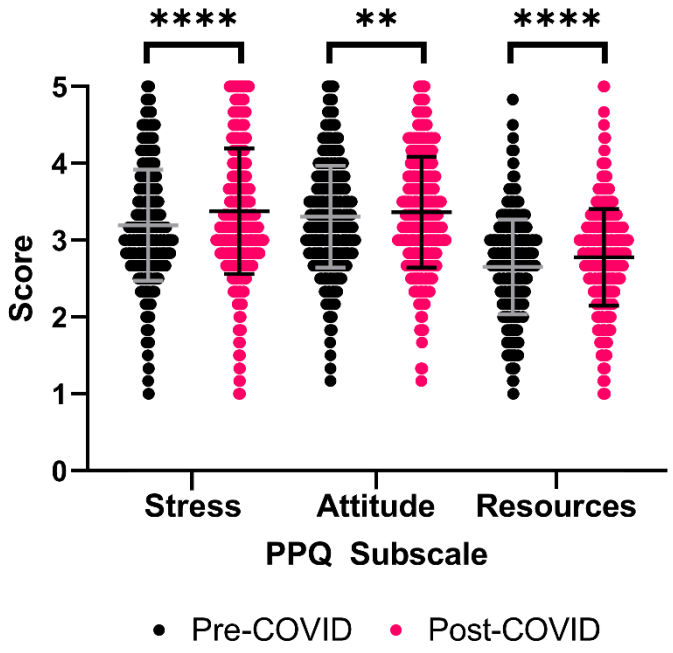

Figure 5.1 Publication pressure questionnaire subscale scores pre- and post-COVID-19 pandemic onset. Paired Student's t-test with Bonferroni correction. ***P=0.0011, **** P≤0.0001. N=1020.

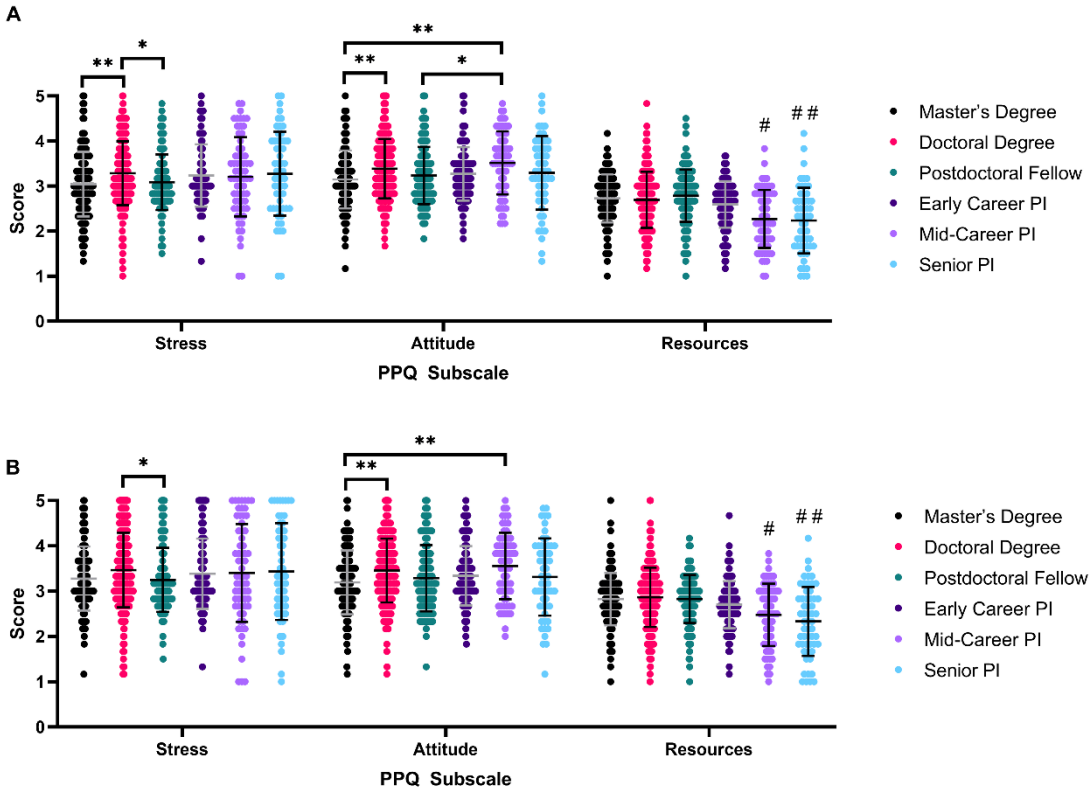

Figure 5.2 Differences in publication pressure questionnaire subscale scores between academic positions. N=1020, one-way ANOVA analysis. * P≤0.05, ** P≤0.01, *** P≤0.001, **** P≤0.0001. PI: Principal Investigator. (A) Scores Pre-COVID. #= significant difference between Mid-Career PI with Master's Degree, Doctoral Degree, and Postdoctoral Fellow (****). Significant difference between Mid-Career PI with Early Career PI (**). ##= significant difference between Senior PI with Master's Degree, Doctoral Degree, and Postdoctoral Fellow (****). Significant difference between Senior PI with Early Career PI (**). (B) Scores Post-COVID. #= significant difference between Mid-Career PI with Master's Degree (**), Doctoral Degree (****), and Postdoctoral Fellow (***). ##= significant difference between Senior PI with Master's Degree, Doctoral Degree, and Postdoctoral Fellow (****). Significant difference between Senior PI with Early Career PI (**).

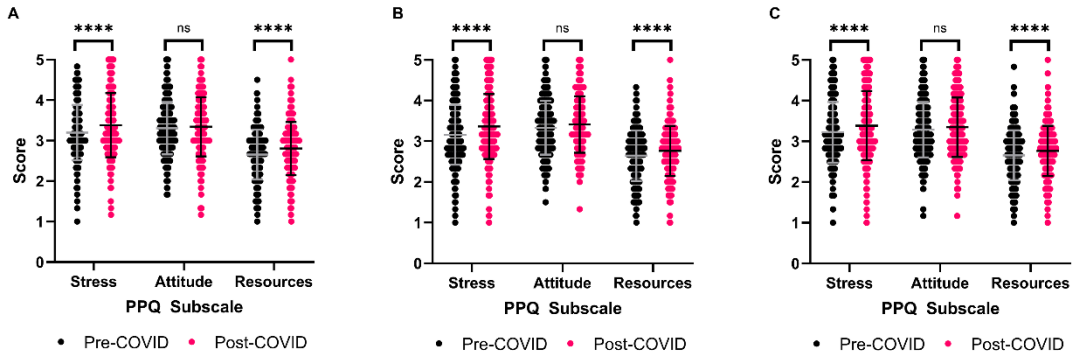

Figure 5.3 Differences in publication pressure questionnaire subscale scores pre- and Post-COVID stratified by research funding agency. Paired Student's t-test with Bonferroni correction. **** P≤0.0001. (A) Canadian Institutes of Health Research respondent scores. N=321. (B) Natural Sciences and Engineering Research Council respondent scores. N=306. (C) Social Sciences and Humanities Research Council respondent scores. N=393.

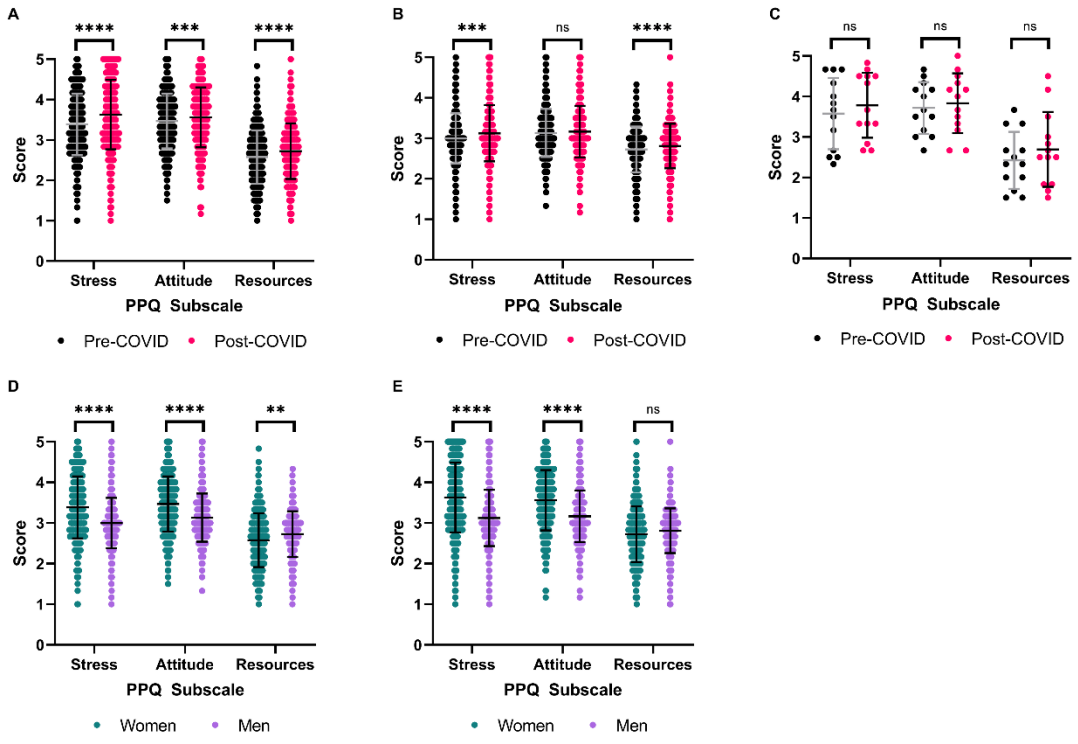

Figure 5.4 Differences in publication pressure questionnaire subscale scores stratified by gender. Paired (A-E) and independent (D-E) Student's t-test with Bonferroni correction. ** P≤0.01, *** P≤0.001, **** P≤0.0001. (A) Respondent Scores from Women. N=484. (B) Respondent Scores from Men. N=462. (C) Respondent Scores from non-binary or genderfluid people. N=13. (D). Pre-COVID subscale score comparison between women and men. N=462-484. (E) Post-COVID subscale score comparison between women and men. N=462-484.

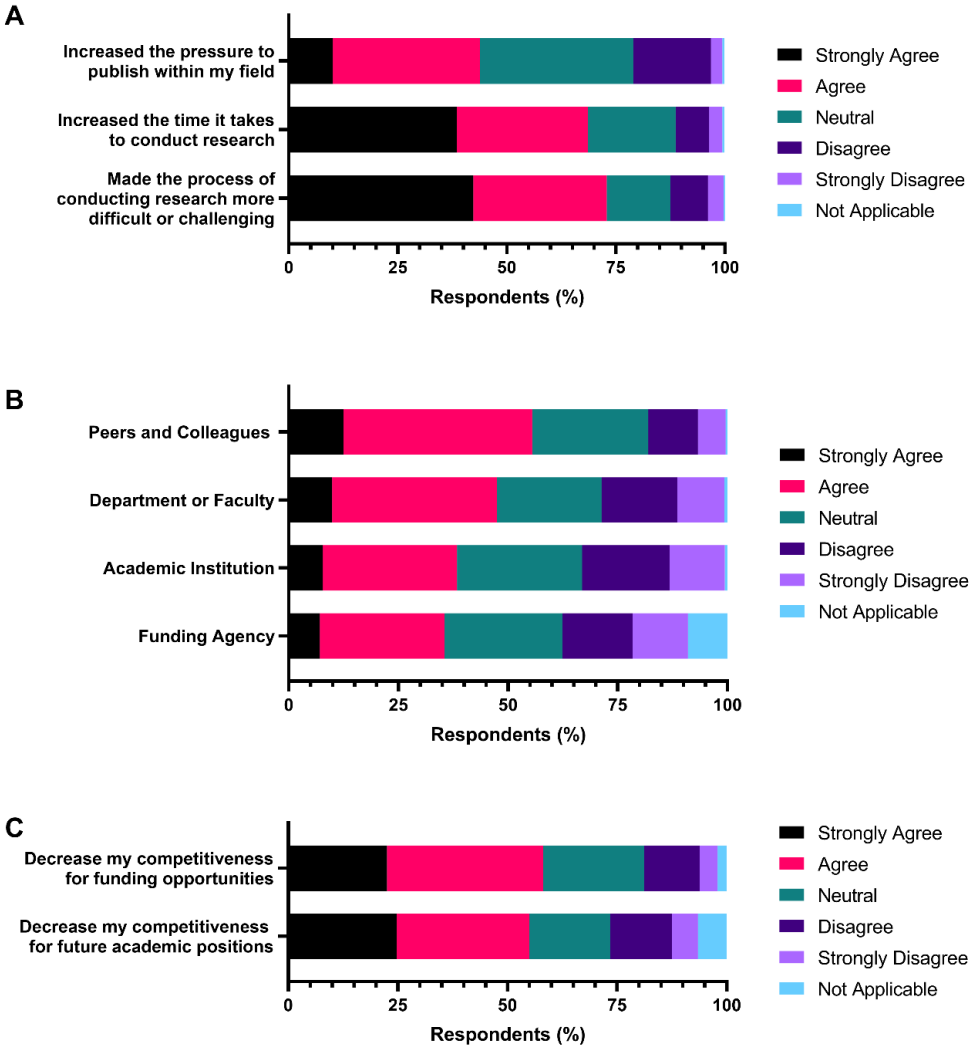

Figure 5.5 Respondent beliefs relating to the impact of the COVID-19 pandemic. Respondents were asked to rate their agreement to a series of questions using the indicated 5-point Likert-type scale, along with the "not applicable" option. N=1020. (A) Respondents' beliefs of how COVID-19 has impacted research within their discipline. (B) Respondents' feelings of support while conducting research during COVID-19. Stratified by the individual or group supporting the respondent. (C) Respondent concerns about how the impact of the COVID-19 pandemic on their publication frequency will impact their competitiveness for future opportunities.

Supplementary Information

All supplementary information is available online.

S1 Appendix. Online Survey Protocol.

S2 Appendix. Minimal Data Set. Demographic values include Academic Position and Research Funding Agency, other demographic information removed for participant confidentiality.

S1 Fig. Publication pressure questionnaire subscale scores by academic position. Paired Student's t-test with Bonferroni correction. * P≤0.05, ** P≤0.01, *** P≤0.001, **** P≤0.0001. (A) Graduate Student: Master's Degree Scores. N= 166. (B) Graduate Student: Doctoral Degree Scores. N=410. (C) Postdoctoral Fellow Scores. N=201. (D) Principal Investigator: Early Career Scores N=121. (E) Principal Investigator: Mid-Career Scores N=66. (F) Principal Investigator: Senior Scores N=66.

S2 Fig. No significant differences in perceived publication pressure experienced by respondents with different research funding agencies. One-way ANOVA, N=306-393. P>0.64 for all comparisons. CIHR: Canadian Institutes of Health Research, NSERC: Natural Sciences and Engineering Research Council, SSHRC: Social Sciences and Humanities Research Council. (A) Scores Pre-COVID. (B) Scores Post-COVID.

S1 Table. Trainee respondent goal career field following completion of studies. N= 777.

S2 Table. Location of respondents' affiliated research institution. N=1020**S3 Table. Respondent ethnicity.** Respondents could select multiple responses. N=1020. These categories were adapted from the Statistics Canada Visible Minority and Population Group Reference Guide, Census of Population (2016) [43]. Examples of respondent descriptions who chose to self-identify include: Biracial or mixed race, Canadian, Jewish, and West Indian.

S4 Table. Publication Pressure Questionnaire Subscale Scores stratified by academic position. Values represent mean score with standard deviation in brackets.

S5 Table. Publication Pressure Questionnaire Subscale Scores stratified by trainee goal career field after studies. Values represent mean score with standard deviation in brackets.

S6 Table. Publication Pressure Questionnaire Subscale Scores stratified by research funding agency. Values represent mean score with standard deviation in brackets.

S7 Table. Publication Pressure Questionnaire Subscale Scores stratified by location. Values represent mean score with standard deviation in brackets.

S8 Table. Publication Pressure Questionnaire Subscale Scores stratified by ethnicity. Values represent mean score with standard deviation in brackets.

Chapter 6: Discussion – The Benefit and Challenges of Interdisciplinarity

Over the last four chapters, you have read seemingly disparate research topics – spinocerebellar ataxia, knowledge translation, and graduate-level education. These each correspond to one facet of my socialization in graduate studies, research, service, and teaching, respectively. On the surface, this combination of topics may seem odd and unrelated. However, not only are they connected through the framework of graduate school socialization, but through the pragmatic common goal of wanting to help people by better understanding a phenomenon. For Chapters 2 and 3, the purpose of this work was to aid and serve ataxia patients and family members. For Chapters 4 and 5, this research was done to support graduate students, postdoctoral fellows, and other academics impacted by the COVID-19 pandemic. Although the end goals of these lines of inquiry were similar, producing research that will assist different populations, the methodology used throughout this dissertation draws on a variety of disciplinary backgrounds. There is no universal approach that will answer all questions. Thus, it is beneficial for one to be familiar with multiple methodologies with which to consider problems. This concept of mixing multiple ways of knowing is the core concept of interdisciplinarity.

The National Science Foundation defines interdisciplinary research as “research by teams or individuals that integrates information, data, techniques, tools, perspectives, concepts, and/or theories from two or more disciplines… to advance

fundamental understanding or to solve problems whose solutions are beyond the scope of a single discipline" (358). Similarly, Ashby and Exter define interdisciplinary education as the "integration of knowledge drawn from diverse disciplines to address problems that cannot be solved by a single disciplinary perspective" (359). Both descriptions highlight the advantage of interdisciplinary approaches to complex or ill-defined problems, as multiple points of view can lead to creative and innovative solutions (359–361). The idea of interdisciplinarity is not a new one, yet there has been little empirical research on the topic (362,363). One barrier to research is that interdisciplinarity is a complex idea in and of itself, one that a single disciplinary perspective cannot explore fully. To begin examining the breadth of interdisciplinarity, typological descriptions have been developed to better define the scope of interdisciplinarity being applied in a particular situation.

Broadly speaking, interdisciplinarity is any activity that spans across traditional disciplinary boundaries (364). However, the degree to which disciplines interact or integrate can vary. For example, cross-disciplinarity describes when theories, tools, or frameworks from one discipline are used within another discipline, with the two disciplines often being related (365). Multi-disciplinarity is when multiple disciplinary approaches are combined to achieve a common goal, but there is still siloing of methodologies such that the component disciplines are still identifiable from one another (365,366). Lastly, trans-disciplinarity is the fusion of disciplinary knowledge, theory, and methodologies to the extent that facets are no longer attributable to a single disciplinary area (365,367). Given these definitions, this

dissertation largely falls under the multi-disciplinary umbrella, as the several disciplinary foundations on which this work is based remain identifiable. Further, there is siloing of different methodologies from each other due to the chapter structure employed within this text.

Similar to other multi-disciplinary researchers, I encountered challenges during my graduate studies directly relating to the interdisciplinary nature of the research and socialization I was undertaking. This included limited explicit interdisciplinary training and mentorship, restricted resources dedicated to interdisciplinary scholarship, and a dearth of knowledge transfer training (368–370).

One frequently cited barrier to interdisciplinary training, and subsequently interdisciplinary research, is that instructors and educational developers are not trained for interdisciplinary teaching (370–373). At the graduate level, many faculty members supervising interdisciplinary projects were themselves socialized in a single discipline, and thus may not have the breadth of expertise to provide support (370). I navigated this challenge by seeking out multiple mentors with different disciplinary expertise. Through receiving feedback and guidance from multiple sources, I was able to better comprehend the various ways I could approach a research question and determine what combination of methodologies would best fit the research context. From these discussions, I developed what Lattuca and colleagues term *appreciation of disciplinary and non-disciplinary perspectives*, that is the awareness of the advantages and gaps offered by multiple disciplinary viewpoints (374). Further, I began to *recognize disciplinary limitations*, a step

where interdisciplinary scholars develop a critical awareness of constraints within disciplinary areas (374). Thus, the challenge of seeking out several disciplinary perspectives as part of my learning process supported my interdisciplinary socialization and skill development.

Another barrier to interdisciplinary education and research is a lack of resources, including tangible resources such as physical space and intangible resources such as funding or protected time (368,369). Interdisciplinarity requires lateral work across departments and research units within a university (368). However, the hierarchical structure of academic institutions often allocates funds within disciplinary silos, with many deans and department heads not willing to commit their own limited resources to activities outside their academic division (368,375). The insular nature of disciplinary communities is further reinforced through professional societies, journals, and funding organizations further reinforcing what is ‘in’ and ‘out’ of scope (373,375). Crossing these disciplinary boundaries is often viewed in a negative light (376). I was fortunate to be in a research environment where interdisciplinary research was not only encouraged, but rewarded. In particular, I had a supportive doctoral supervisor, which has been shown to have a major impact on interdisciplinary socialization and success (23,370,377). Though internally interdisciplinary development was seen as a strength, finding funding to support this research has proven a challenge. This is a known barrier, and while grant money explicitly allocated to interdisciplinary inquiry by the Canadian Tri-

Council funding agencies is increasing, it remains little compared to what is available for more traditional forms of research (369).

A final barrier to interdisciplinary is limited training on knowledge transfer and integration for students and faculty (378,379). In short, academics are socialized on how to communicate with other researchers and what means of disseminating knowledge are the most important (24), however, we have not traditionally trained academics to communicate with other scholars outside their discipline or outside of the academy (380,381). Although efforts to improve researchers' communication with lay audiences have increased over the past decades, cross-disciplinary knowledge transfer and integration remain undervalued (379,380). Like many doctoral students, my expertise in knowledge transfer and integration was mainly developed through trial, error, and self-teaching (368,382). This was further supported through courses within my department focusing on communication, science communication training through graduate student networks, and pursuing a postgraduate certificate in knowledge mobilization through the University of Guelph (383). These skills in how to connect with different audiences, and implicit assumptions made through communication by different disciplines, not only aided my research efforts but also navigate the two previously outlined challenges associated with interdisciplinary.

These challenges associated with interdisciplinarity can, in part, explain the limited number of interdisciplinary undergraduate and graduate programs in Canada (369). For interdisciplinary graduate programs, these are often described as

'choose your own adventure' degrees, where the onus is on the student to seek out appropriate training, mentorship, and integration of research beyond what is expected of single-discipline degree seekers (369,384). There is also minimal support for disciplinary students who wish to prepare for future interdisciplinary collaborations in addition to their primary research focus. Indeed, a survey of over 4,000 doctoral students from the United States, across multiple research focuses and universities, revealed only 27% felt that their training had prepared them for interdisciplinary work (385).

However, there have been efforts to increase interdisciplinary education and research. This includes the creation of new training programs for students, research networks for faculty, dedicated funding streams, and physical centres for interdisciplinary research (369,386–388). Research into the outcomes of incorporating interdisciplinarity into research and education continues to be positive. Through exposure to multiple disciplines, students develop critical thinking and appraisal skills, in addition to proficiency with innovation, communication, teamwork, and conflict management (11,359,368,370). These skill sets help to nurture the researcher of tomorrow to tackle complex problems which border multiple fields of study (360,361). This ability to appraise problems from multiple points of view, and approach solutions through multiple strategies, has helped me become more adaptable to the ever-changing research landscape, particularly during the COVID-19 pandemic. My hope is that my interdisciplinary graduate training continues to serve me well in the years to come.

Future Avenues of Research

Regarding the potential next steps, the work within this dissertation lays the groundwork for multiple future lines of inquiry. For Chapter 2, future work should further explore mechanisms of DNA repair and dysfunction within SCA1 model systems and human cell lines. This includes identifying potential deficits in base excision repair poly(ADP-ribose)ylation in SCA1, as well as further exploring ATM kinase as a therapeutic target. Initial exploration of dysfunctional poly(ADP-ribose) responses within SCA1 has been encouraging (Appendix A), nonetheless, further experiments clarifying mechanisms of action are required.

For Chapter 3, as our 2020 study focused on knowledge translation of ataxia research broadly, there are opportunities for lines of inquiry on specific knowledge translation strategies. For example, other neurological disease researchers have examined what styles and components of lay summary articles best fit the needs of their patient populations (142,389–391). Similar work has not previously been done centring on the experiences of ataxia patients. Further, we should examine what aspects of text-based accessibility improve or hinder ataxia patients' ability to engage with research summaries. This includes, but is not limited to font size, colour contrast, layout consideration, and image use (392).

For Chapters 4 and 5, this research only began to scratch the surface of how graduate students, postdoctoral fellows, and principal investigators have been impacted by COVID-19. Further research should focus on how researchers have managed the transition back to in-person work, as well as trends and disparities in

publication pressure. This work, and other examinations of graduate student and postdoctoral fellow training in laboratory environments, can contribute to current gaps in the literature on STEM trainee socialization.

Conclusions

The work presented in this dissertation covers a variety of research topics using a range of methodologies. They weave an intricate tapestry of interdisciplinary exploration and training that I have had the privilege to experience over the past six years. This makes me a 'surfer' researcher according to Pandya's metaphor for interdisciplinary research (393). They argue that most researchers are 'divers' who plunge deep into a narrow section of the ocean that is knowledge, while surfers travel across the ocean to connect and make relevant the research treasures brought up from the deep by the divers. The argument that Pandya makes, and one which I have echoed throughout this dissertation, is that the integration of knowledge and its application to develop practical solutions is a key component of the research process. These lessons on interdisciplinarity and skills I have developed throughout my graduate studies have fundamentally shaped my identity as a scholar, for which I will forever be grateful. With that, I will leave you with a common adage which summarizes the goal of this dissertation, but whose linguistic origin has been lost to time:

"Jack of all trades, Master of none, but better than a Master of one"

– Author Unknown

Appendix A: Evidence of Poly(ADP-ribose) Dysregulation within Spinocerebellar Ataxia Type 1

Introduction

Poly(ADP-ribose) (PAR) is a post-translational modification added to sites of DNA damage by PAR polymerases (PARPs) (394). These long branching chains of repeating ADP-ribose molecules help to regulate multiple biological processes, such as the recruitment of DNA repair proteins to damaged areas or initiating cell death via parthanatos (395). PAR is added to sites of damage, as well as to proteins involved in DNA repair, following demining events such as oxidative stress (394,395). The creation of PAR is incredibly energy-intensive, with PAR chains rapidly catabolized by poly(ADP-ribose) glycohydrolase (PARG) following successful DNA repair (396,397). If PAR chains are not catabolized, PARP will remain activated and continue to deplete cellular stores of NAD+ and ATP to generate PAR, resulting in a cellular energy crisis (398).

Hyperactivated PAR responses and PARP dysfunction has been linked to multiple forms of neurodegeneration including Alzheimer's Disease, Parkinson's Disease, Huntington’s Disease, and Spinocerebellar Ataxia Type 3 (399–403). Our group has shown that huntingtin binds to PAR *in vitro* and that there are elevated PAR levels in fibroblasts derived from HD patients (403). This is consistent with previous DNA damage phenotypes we have observed in HD (115,117). Animal models of HD and HD patients are known to experience muscle wasting in the late stages of

disease, which is consistent with energy depletion associated with the PAR energy crisis phenotype (404–406).

Despite the analysis of PAR and PARP within other neurodegenerative diseases, there has been little exploration within the SCA1 context. *In silico* network analysis has suggested that PARP1 has a positive impact on the lifespan of ATXN1[Q84] *Drosophila* (407). However, this work has not been followed up with biological confirmation. Although not as extensively studied as HD, both SCA1 patients and mouse models also exhibit a wasting phenotype (84,408).

Rationale

We know there is a high degree of similarity between HD and SCA1 regarding symptoms and pathology (116). This is in part why our lab uses a comparative approach when researching these disorders. If there are DNA damage markers altered with the HD context, we will examine if there is similar dysregulation within SCA1 and vice versa. We have had success using this comparative approach to examine the DNA damage response of ataxin-1 in contrast to huntingtin (117,121). Thus, as there is significant evidence of PAR dysregulation in HD, we took a similar approach to assess if there is similar dysregulation of PAR in SCA1.

Preliminary data supports our hypothesis of PAR dysregulation in SCA1 compared to healthy fibroblasts. This supports further experiments be undertaken to clarify potential mechanisms to explain dysregulated PAR and PARP activity within SCA1 fibroblasts and model systems.

Materials and Methods

Unless otherwise specified, protocols and reagents used in Appendix A are identical to those outlined in Chapter 2.

Reagents

All reagents were sourced from Sigma-Aldrich unless otherwise specified.

Anti-PAR Immunofluorescence of Fibroblast Cell Lines

hTERT-immortalized TruSCA1-Q52Q29M (SCA1), TruHD-Q21Q18F (wildtype), and TruHD-Q43Q17M (HD) fibroblast cells were treated with either phosphate-buffered saline (PBS) supplemented with calcium and magnesium, 10μM of PARG inhibitor PDD00017273, 30 minutes of 100mM $KBrO_3$, or a combination of the PARG inhibitor and potassium bromate conditions (203). Potassium bromate is used as an oxidative stress agent to trigger a PAR response. As PAR formation is highly transient, the PARG inhibitor PDD00017273 was used to prevent the degradation of PAR. Cells are fixed with 4% paraformaldehyde and PAR levels are measured by immunofluorescence with MABE 1031.

Purified 3X FLAG-Ataxin-1 Generation

A set of 3X FLAG- ataxin-1 constructs (ataxin-1 Q30, ataxin-1 Q85, ataxin-1 Q85 S776A, and ataxin-1 Q15 dAXH) were obtained from the Zoghbi Laboratory at the Baylor College of Medicine (97). These constructs were transfected into HEK293 and purified via pulldown with M2 FLAG agarose affinity gel, followed by FLAG

elution with 150 ng/µL FLAG peptide in a 0.5 M Tris HCL and 1 M NaCl solution at pH 7.5. Protein concentrations were determined via Bradford assay (409).

PAR Overlay Assay of Ataxin-1

5 pmol purified ataxin-1 protein, positive control histone H1, and negative control bovine serum albumin (BSA) are dotted on a nitrocellulose membrane and then incubated with purified PAR polymer for 1 hour (410). Histone H1 was used as a positive control as it has strong PAR binding, while BSA was used as a negative control as it has no PAR binding ability (411). The nitrocellulose membrane is rinsed with tris-buffered saline with 0.1% Triton X-100 and 300mM NaCl for 30 minutes to remove excess PAR polymer. Next, protein immunoblotting was conducted with an anti-PAR antibody (Sigma Millipore, MABE 1031) to detect any PAR bound to the protein samples (410,411). Amido Black 10b protein stain was applied following immunoblotting to ensure proper protein loading (121,412).

Co-Immunoprecipitation of eGFP-ataxin-1 and PAR

RPE1 cells were transfected with eGFP-ataxin-1 Q26 or eGFP-ataxin-1 Q84 at incubated at 37°C for 24 hours. These cells were then with either supplemented PBS (control) or 100µM H_2O_2 for 10 minutes at 37°C. Cells were trypsinized, resuspended in PBS, then fixed with 1% PFA for 10 minutes. The fixation reaction was quenched with 1M glycine, then lysed in RIPA buffer (50 mM Tris-HCl pH 8.0, 150 mM NaCl, 1% NP-40, 0.25% sodium deoxycholate, 1 mM EDTA, protease and phosphatase inhibitors (Roche). Input samples were acquired, then the remaining

lysates were incubated anti-GFP (Abcam, AB6556) and protein A sepharose beads overnight with rotation at 4°C. Beads and proteins were washed three times with RIPA lysis buffer, then denatured with SDS-loading buffer at 100°C for 10 minutes. Samples were separated by SDS-PAGE and analyzed by western blot with anti-ataxin-1 (Zoghbi Lab, MABN2542) and anti-PAR (Sigma Millipore, MABE 1031).

Results

SCA1 fibroblasts are hypo-PARylated under control conditions, hyper-PARylated following oxidative stress and PARG inhibition

To begin investigating potential PAR dysregulation within the SCA1 context, we measured levels of PARylation in SCA1 fibroblasts compared to wildtype and HD fibroblasts (Figure 1). We hypothesized that, similar to HD fibroblasts (403), SCA1 fibroblasts would have increased PAR production following PARG inhibition or oxidative stress, leading to a state of hyper-PARylation. However, SCA1 cells were hypo-PARylated in control and PARG inhibition conditions, with less PAR signal than wildtype or HD fibroblasts (Figure 1). There was no significant difference in PAR signal between wildtype and SCA1 fibroblasts following oxidative stress treatment, although SCA1 cells continued to have a lower signal than HD fibroblasts (Figure 1). Only through a combination treatment of oxidative stress and PARG inhibition did SCA1 fibroblasts display higher PAR levels than wildtype cells, with no significant difference between SCA1 and HD cell lines (Figure 1). These results suggest that SCA1 fibroblasts have a slowed or reduced PAR response,

with elevated levels of PARylation only becoming apparent when PARP1 activity is increased with oxidative stress and PARG activity is inhibited.

Ataxin-1 bind PAR *in vitro*, expanded polyglutamine tract ataxin-1 constructs display less binding affinity than wildtype length constructs

Following initial evidence of PAR dysregulation in SCA1 fibroblasts, next we asked if the ataxin-1 protein can bind PAR chains *in vitro* via PAR overlay assay (411). Due to the similarities in structure between PAR and RNA, many oligonucleotide binding folds have been documented to bind PAR (413). For this reason, we predicted that if ataxin-1 binds PAR, it would do so through the oligonucleotide binding fold within the AXH domain. To test this hypothesis, we used a set of FLAG-ataxin-1 constructs designed by the Zoghbi lab (ataxin-1 Q30, ataxin-1 Q85, ataxin-1 Q85 S776A, and ataxin-1 Q15 dAXH) to assess protein-protein interactions of ataxin-1 (97). We chose this construct set as it included an AXH domain deletion mutant. We predicted that the wildtype (ataxin-1 Q30) and expanded (ataxin-1 Q85, ataxin-1 Q85 S776A) constructs would have similar PAR binding ability, while the AXH deletion mutant (ataxin-1 Q15 dAXH) would have reduced or no binding ability. We included the ataxin-1 Q85 S776A construct as it was part of the initial set, but did not think this mutation would impact PAR binding as S776 in ataxin-1 is not directly involved with RNA binding.

We again found surprising results. Although ataxin-1 had *in vitro* PAR binding ability, our predictions of which constructs would be able to bind ataxin-1 were

incorrect (Figure 2). From visual inspection alone (Figure 2A), it was clear that the polyglutamine expansion ataxin-1 constructs bound less than their wildtype length counterparts. This was further confirmed through quantification and statistical analysis (Figure 2B), where the ataxin-1 Q85 and ataxin-1 Q85 S776A constructs had significantly less PAR binding compared to wildtype ataxin-1 Q30. Furthermore, the deletion of the AXH domain seemed to not affect PAR binding, with no significant difference between ataxin-1 Q30 and ataxin-1 Q15 dAXH (Figure 2B). These results support that ataxin-1 has a PAR binding domain but suggest that PAR binding is independent of the AXH domain. Further, this data implies that polyglutamine expansion could interfere with ataxin-1 PAR binding.

Preliminary co-immunoprecipitation data suggest polyglutamine-expanded ataxin-1 is less PARylated than wildtype protein

After examining the potential ability of ataxin-1 to bind PAR *in vitro*, next we wanted to examine its potential for PARylation, also known as PolyADP-ribosylation or the process of having PAR chains covalently bonded to proteins by PARPs, and its interaction with PARylated proteins (394). To examine the PARylation of ataxin-1, we performed a co-immunoprecipitation of wildtype and polyglutamine ataxin-1 under basal and oxidative stress conditions with 100µM H_2O_2. Initial replicates were attempted with FLAG-ataxin-1 Q30 and FLAG-ataxin-1 Q85, however, we had issues with the reproducibility of findings. We hypothesis that the 3X FLAG tag may have disrupted the liquid-liquid phase separation of ataxin-1, which would modify its protein interactions *in vivo* and explain the variability we observed (414).

Thus, we changed to eGFP-tagged ataxin-1 constructs for this experiment, as others have demonstrated GFP does not interfere with ataxin-1 liquid-liquid phase separation (100,414).

Co-immunoprecipitation replicates with eGFP-ataxin-1 Q26 and eGFP-ataxin-1 Q84 showed decreased variability between replicates. Consistent with the literature, polyglutamine-expanded ataxin-1 had lower expression than wildtype ataxin-1 (Figure 3). Preliminary findings indicate wildtype ataxin-1 has less PARylation than polyglutamine expended ataxin-1 (Figure 3). Further replicates will be needed to quantify this phenotype.

Discussion and Conclusion

Overall, these initial results support further exploration of PAR dysregulation within SCA1 cell models. Our immunofluorescence data taken together with our past results documenting increased oxidative DNA damage markers in SCA1 cells following stress (121), this data implies that although SCA1 fibroblasts may have increased DNA damage, a slowed PARP1 response is leading to lower levels of PAR. Further, the complementary data from the PAR overlay assay, showing ataxin-1 with polyglutamine expansion has reduced PAR binding *in vitro* compared to wildtype, and co-immunoprecipitation experiments, indicating polyglutamine-expanded ataxin-1 is less PARylated at basal and oxidative stress conditions *in vivo*, suggest the polyglutamine tract in ataxin-1 influences its interaction with PAR.

However, further experiments are needed to clarify the underlying mechanisms which contribute to this dysfunctional PAR response. This includes further replicates of co-immunoprecipitation data, as well as PAR overlay assays with additional ataxin-1 constructs with disease-relevant mutations such as the ATM phosphorylation site (121). Given these results suggest polyglutamine-expanded ataxin-1 contributes to a dysfunctional PAR response, we must also ask if we can correct these phenotypes by removing or reducing total levels of the expanded ataxin-1 protein. Such analysis would provide further support that it is the ataxin-1 protein specifically contributing to the dysfunction, as opposed to other factors.

To accomplish this, I propose the examination of PAR levels by immunofluorescence in TruSCA1-Q52Q29M cells following siRNA knockdown of ataxin-1, under conditions of oxidative stress and PARG inhibition, compared to TruSCA1-Q52Q29M with a scrambled siRNA treatment. This would allow us to assess PAR levels at varying levels of ataxin-1 knockdown, and determine if PAR levels observed correlate with relative ataxin-1 expression. The proportion of ataxin-1 knockdown by siRNA would need to be confirmed by western blot analysis. Other markers we could assess in addition to PAR include markers of oxidative stress, such as 8-oxo-dG, to determine if there are decreased DNA damage indicators in TruSCA1-Q52Q29M cells with reduced ataxin-1. Similar experiments could also be conducted with transfected eGFP-ataxin-1 constructs with disease-modifying mutations such as eGFP-ataxin-1 Q26 S186AS188S or eGFP-ataxin-1 Q84 S776A, complementing the previously proposed experiments

with endogenous ataxin-1. This two-pronged approach would provide further evidence that polyglutamine-expanded ataxin-1 is the main driving force behind PAR dysregulation.

These experiments align with a growing trend in the SCA1 field of identifying the correction of a measurable phenotype following the reduction of ataxin-1 protein levels (91). This identification of biomarkers that correlate with ataxin-1 protein levels is of growing interest due to the development of ataxin-1 antisense oligonucleotide technology (102,415). This previous work has focused on mouse model related phenotypes (climbing ability, lifespan, weight) or neuronal cell health (size, shape, density) (91,102,415). The identification of DNA damage-related markers, such as 8-oxo-dG and PAR, would be a novel contribution to the field.

Figures

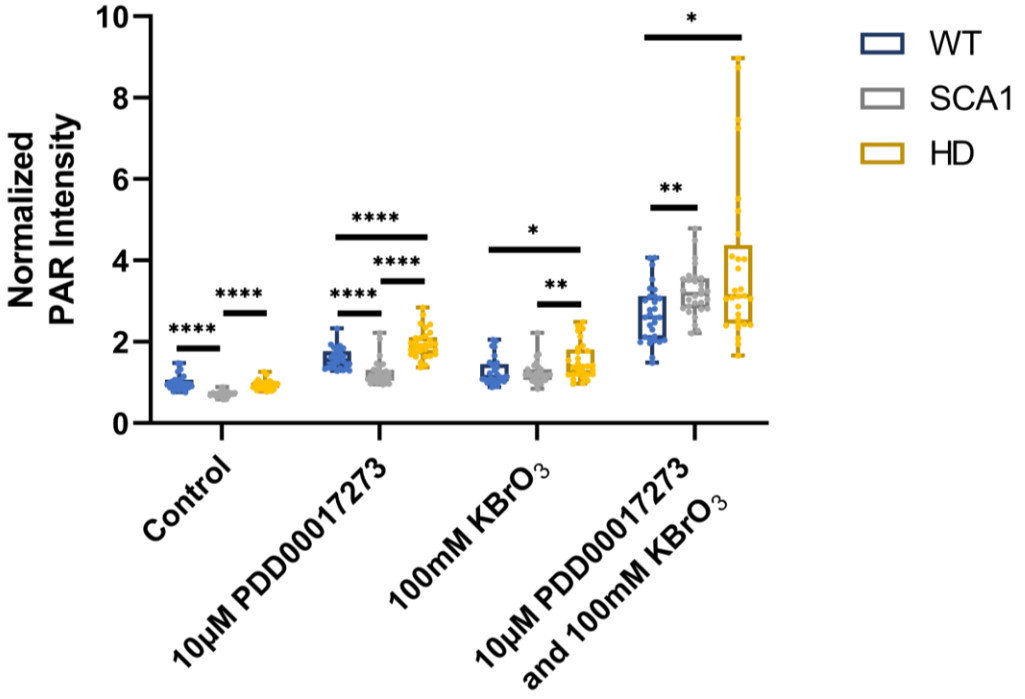

Figure AP1. **Poly(ADP-ribose) levels in SCA1, HD, and healthy fibroblasts following oxidative stress treatment.** N=3, n=29-30, with 20-50 cells per image. WT: TruHD-Q21Q18F, SCA1: TruSCA1-Q52Q29M, HD: TruHD-Q43Q17M. Indicated cell lines treated with either supplemented PBS, 10μM PDD00017273, 100mM KBrO3, or 10μM PDD00017273 and 100mM KBrO3. Cells were fixed with 4% PFA and immunofluorescence was conducted with rabbit anti-PAR antibody (MABE 1031). Imaged at 20x on a Nikon C2 Widefield Microscope, quantified using CellProfiler. All graphs display mean (±SD). Significance values calculated by multiple Mann-Whitney analyses with correction for multiple comparisons, *P ≤ 0.05, **P ≤ 0.01, *** P ≤ 0.001, **** P ≤ 0.0001.

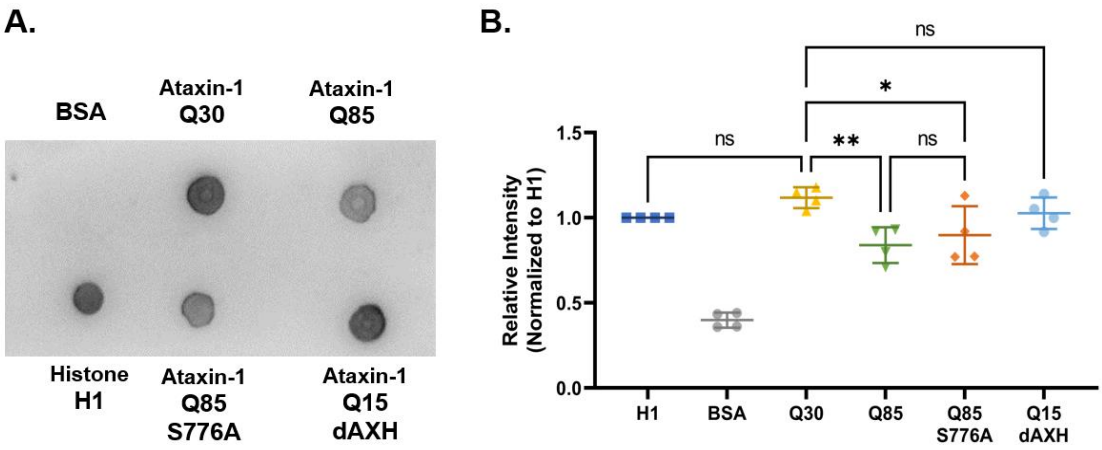

Figure AP2. **PAR overlay assay of FLAG-ataxin-1 constructs suggests polyglutamine tract length influences PAR binding.** N=4. H1: Histone H1, BSA: Bovine serum albumin, Q30: Ataxin-1 Q30, Q85: Ataxin-1 Q85, Q85 S776A: Ataxin-1 Q85, 15 dAXH: Ataxin-1 Q15 with deletion of the AXH domain. A dot blot was performed with 10pmol of the indicated samples on nitrocellulose. An anti-PAR western blot analysis was conducted with MABE 1031. **A.** Representative dot blot. **B.** Quantified results. Quantified using ImageJ, raw values normalized to histone H1 signal. Error bars display mean (±SD). Significance values were calculated by one-way ANOVA, *P=0.0412, **P=0.0067. All values were significantly higher than BSA p<0.0001.

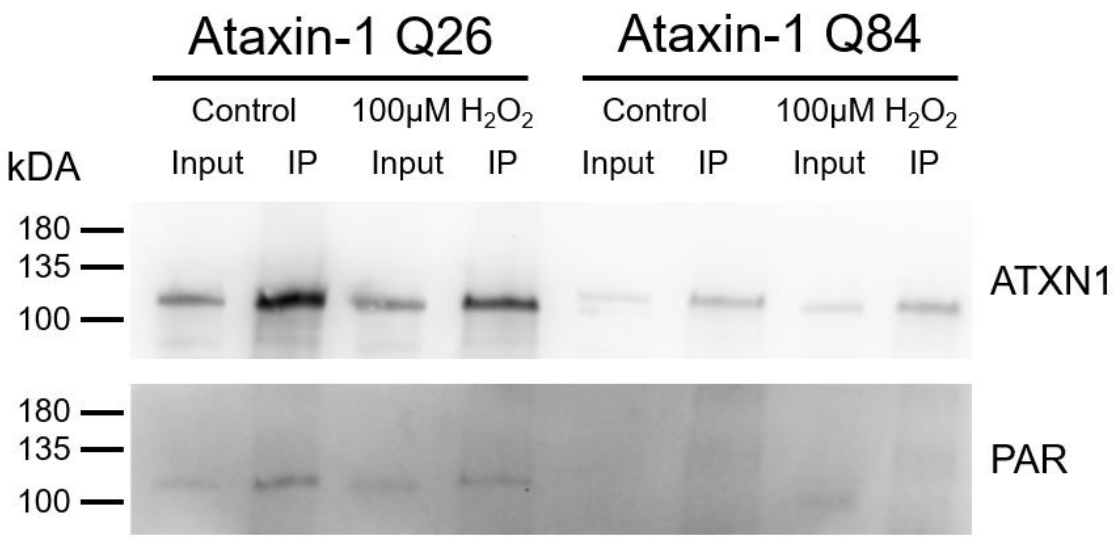

Figure AP3. **Co-Immunoprecipitation of GFP-ataxin-1 suggests wildtype length protein is PARylated.** RPE1 cells were transfected with indicated construct and incubated for 24h, then treated with PBS or 100μM H_2O_2 for 10 min, fixed with 1% PFA for 10 min, quenched with 125mM glycine for 5 min, then lysed in RIPA buffer. Lysates were incubated with the GFP antibody AB6556, rinsed with excess RIPA buffer, separated by SDS-PAGE, then immunoblotted with anti-ataxin-1 (Zoghbi MS 534) and anti-PAR (MABE 1031). Image is representative of two replicates.

Appendix B: Additional Writing and Contributions

During my graduate studies, I had the privilege of contributing to multiple scholarly initiatives at McMaster University and beyond. I completed these activities in my role as PhD student, lead Educational Development Fellow at the MacPherson Institute, or Managing Editor at SCAsource. Below are some of the highlights of this work, which could not be included in full in this dissertation.

Primary Research Articles

Tsirulnikov D*, **Suart C***, Ream A, Vulcu F, Mullarkey CE. Game On: Virtual laboratory simulation improves student learning outcomes & motivation. FEBS Open Bio. 2023 Feb 1;13(3)396-407. doi: 10.1002/2211-5463.13567 (Co-First Authorship)

de Bie A, Dhanoa J, Ing E, Mordell D, **Suart C**. The first 80 years of teaching and learning at McMaster University, 1890-1970. Where learning deeply matters: Reflections on the past, present, and future of teaching at McMaster University. 2022 Dec 7;1(1). doi: 10.15173/mi.v1i1.5370

Suart C, Nowlan Suart T. Navigating dynamic positions of power in a student-student research partnership. International Journal for Students as Partners. 2022 Oct 18;6(2):121-7. doi: 10.15173/ijsap.v6i2.5110

Suart C, H— J. You count too: Reflections on navigating dual identities as disabled students and teaching assistants. Dis/orientation: Navigating accessibility in teaching & learning [Zine]. 2022.

Goss S, Barba Bazan C, Neuman K, Peng C, Begeja N, **Suart C**, Truant R. Mod3D: A low-cost, flexible modular system of live-cell microscopy chambers and holders. PLOS One. 2022 Jun 3;17(6):e0269345. doi: 10.1371/journal.pone.0269345

Book Chapters

Brown K, de Bie A, Mordell D, **Suart C**. Online and Technology-Enabled Learning. In: Brown K, de Bie A, editors. Forward with FLEXibility: A teaching and learning resource on accessibility and inclusion. Pressbooks; 2021.

Lay Articles

Suart C. "Nothing About Us Without Us": Forming collaborative partnerships with disabled students to improve digital accessibility. Spotlight on SoTL. 2022 November 19.

Suart C. Bringing the Rocks to the People: The Creation of a Virtual Geological Field Trip. Spotlight on SoTL. 2022 July 25.

Suart C. "To watch or not watch the recording": Exploring student engagement with online learning material. MI Picks Volume 3. 2021 May 5.

Suart C. Connecting Across Virtual Space: Creating Community through Care. MI Picks Volume 2. 2021 March 29.

Suart C. What Would Paulo Freire Think of Avenue to Learn? Critical Pedagogy in an Age of Online Learning. MI Picks Volume 1. 2020 December 2.

Suart C. Snapshot: What are Preprints? SCAsource. 2020 April 3.

Flower M, **Suart C.** New molecule can reverse the Huntington's disease mutation in lab models. SCAsource. 2020 May 8.

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Babi M, Neuman K, Peng CY, Maiuri T, **Suart CE**, Truant R. Recent microscopy advances and the applications to Huntington's disease research. Journal of Huntington's Disease. 2022 Jan 1;11(3):269-280. doi: 10.3233/JHD-220536

Maiuri T, Hung CL, **Suart C**, Begeja N, Barba-Bazan C, Peng Y, Savic N, Wong T, Truant R. DNA repair in Huntington's disease and spinocerebellar ataxias: Somatic instability and alternative hypotheses. Journal of Huntington's Disease. 2021 Jan 1;10(1):165-73. doi: 10.3233/JHD-200414

Maiuri T, **Suart CE**, Hung CL, Graham KJ, Barba Bazan CA, Truant R. DNA damage repair in Huntington's disease and other neurodegenerative diseases. Neurotherapeutics. 2019 Oct;16(4):948-56. doi: 10.1007/s13311-019-00768-7

Working Papers and Reports

Harvey K, **Suart C**, Aspenlieder E, Evanovitch J, de Bie A, Cassidy-Neumiller M, Karim F, Minhas A, Krone J. Results from an Environmental Scan of Teaching and Learning Scholarship Across McMaster University. Hamilton (ON): MacPherson Institute; 2022. 35 p.

Dyce L*, Ogrodnik *, **Suart C***, van Gastel, G, Storm E, Goff L. McMaster University Fall Experience Survey Report. Hamilton (ON): MacPherson Institute; 2020. 49 p. (Co-First Authorship)

Suart C, Clarke S, Sherwani A, Wong V, de Bie A. Knowledge exchange initiative of teaching research at post-secondary institutions: Similarities and differences across disciplines. Hamilton (ON): MacPherson Institute; 22019. 5 p.

Teaching

Module Instructor, University of Toronto Mississauga Fall 2022
General Laboratory Protocols (Program for Accessing Research Training)

Teaching Assistant, McMaster University Fall 2020, Fall 2021, Fall 2022
Emerging Discovery in Cell Biology (BIOCHEM 3CB3)

Course Instructor, McMaster University Winter 2021
Essential Skills in Teaching and Learning (I) (EDUCATN 600)

Guest Lecturer, McMaster University Fall 2019, Winter 2020
Essential Skills in Teaching and Learning (II) (EDUCATN 700)
Lesson Title: Seven Research-based Principles for Smart Teaching

Teaching Assistant, McMaster University Fall 2018, Fall 2019
Research Advances in Cell Biology and Biochemistry (BIOCHEM 3EE3)

Guest Lecturer, McMaster University Summer 2018
Principles and Practices of University Teaching (EDUCATN 750/751)
Lesson Title: Accessible Active Learning

PhD Thesis – C. Suart; McMaster University – Biochemistry & Biomedical Sciences

Workshop and Module Development

Science Dissemination to Lay Audiences November 2022

International Congress for Ataxia Research

Leading Effective Labs Module Fall 2021

McMaster University Mandatory TA Training

Universal Design for Learning and Accessibility Module Fall 2021

McMaster University Professional Development for Teaching Series,

Teaching Effectively Online August 2020

McMaster Teaching and Learning Forum

Universal Design for Learning Module Spring/Summer 2020

Learning to Teach Online

Teaching Philosophy Statement Module Fall 2019

EDUCATN 600: Essential Skills in Teaching and Learning (I)

Conference Organization

Gordon Research Seminar Chair 2019 – 2023

2023 CAG Triplet Repeat Disorders GRS, Gordon Research Conferences

Trainee Organising Committee Member 2021 – 2022

2022 International Congress for Ataxia Research, Trainee Organising Committee

BBS Research Symposium Student Co-Chair 2020 – 2022

2021 & 2022 Biochemistry & Biomedical Sciences Research Symposiums, McMaster University

Early Career Researcher Day Co-Chair 2020 – 2021

2021 Expanded Repeat Conference, United Kingdom Dementia Research Institute

BBS Research Symposium Communications Committee Chair 2019 – 2020

2020 Biochemistry & Biomedical Sciences Research Symposium, McMaster University

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