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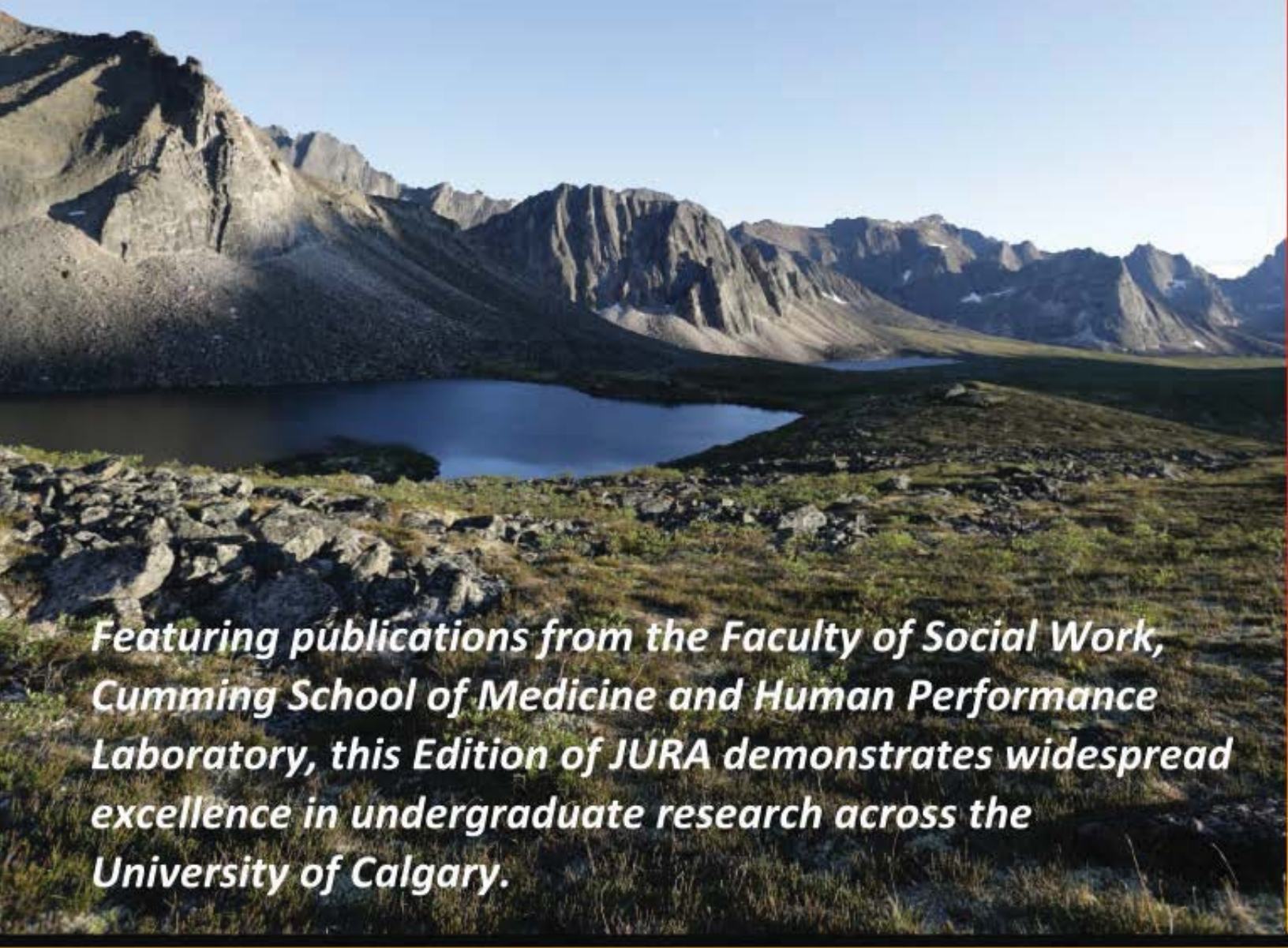

Featuring publications from the Faculty of Social Work, Cumming School of Medicine and Human Performance Laboratory, this Edition of JURA demonstrates widespread excellence in undergraduate research across the University of Calgary.

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Volume 5, 2015

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Journal of Undergraduate Research in Alberta

Welcome to the Fifth Edition of the Journal of Undergraduate Research in Alberta. This Edition of JURA showcases some exceptional undergraduate research covering a diverse range of topics. We are pleased to introduce the first Feature Article in this edition of JURA, demonstrating direct relevance of undergraduate research at the University of Calgary to residents of Alberta. Child welfare practices in Alberta are addressed in this three-part feature article which is summarized below.

Prior to 1998, there were relatively little child welfare data to support the shifts and innovations in child welfare policy, legislation and practice in Canada. Rather, policy and practice decisions were based upon established value positions related to the best interests of the child, or in response to tragic events or child fatalities. The Canadian Incidence Study of Reported Child Abuse and Neglect (CIS-1998) provided the initial opportunity to examine contextual factors associated with child welfare decision making. Jurisdictional variation in policy and practice supported the development of provincial and territorial studies that ran concurrently with each national CIS cycle. The Alberta Incidence Study of Reported Child Abuse and Neglect (AIS-2008) produced a provincial estimate of 27,147 child investigations which serves as a solid foundation on which to understand the context and outcomes of child investigations in this province. Secondary data analyses of the AIS-2008 provide an opportunity to explore child, parental, household and case factors associated with child maltreatment investigations as well as outcomes related to placement, child welfare court, ongoing services and case substantiation. This special issue highlights secondary analyses of the AIS-2008 on three child welfare research and practice topics. These specific analyses examine the risk and protective factors associated with differential forms of front-end investigation; the increase of younger children at risk (0-5 years of age); and the continuing emergence of intimate partner violence as a form of maltreatment. Findings from the AIS-2008 analyses inform policy and practice for Alberta Human Services.

-Adrian Yee

We would like to thank all of the authors, reviewers and Editorial Board Members who made publication of the fifth edition of JURA possible. Lastly, we would like to acknowledge Dr. Walter Herzog who has continued to provide mentorship and financial support to JURA as well as Dr. Mike Kallos, who has taken an active role in the expansion of JURA on the University of Calgary Campus.

JURA is always looking for authors, reviewers, advocates and anyone who may be interested in joining the Editorial Team! We hope that you enjoy the fifth Edition.

Sincerely,

Krysta Powers & Kelsey Collins
Journal of Undergraduate Research in Alberta Editors

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Feature Article Part 1: Differential Response and Traditional Protection Investigation: a Comparision of Two Child Welfare Investgation Streams

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Introduction

Determining an appropriate threshold for which children and families should receive child welfare services has been widely debated in literature. Parental rights, family preservation, and safety of the child are some of the competing interests in the child welfare model that investigating workers must balance[2,9]. Child welfare workers are faced with multiple child welfare orientations when determining the appropriate level of intrusiveness during child maltreatment investigations[3].

Differential Response (DR) model is a flexible approach to child maltreatment investigations developed to provide a range of customized investigative streams incorporating family-centered and strengths-based practices[4]. DR models are an alternative to the Traditional Protection Investigation (INV), which provides a forensic approach to child welfare investigations despite the level of risk of a family. This model is less intrusive compared to INV and is intended for cases that do not present imminent risk to the child,[5,7]. There is a high degree of jurisdictional variation in screening, intake and administration of DR models resulting in a disparity of findings throughout child welfare research [4]. In an attempt to address these disparities, in 2002, the Alberta Response Model was created to provide flexible investigative streams to families based on the type and severity of child maltreatment[1,8]. This Family Enhancement Program works as part of the Alberta Response Model to provide children and families with a DR investigation stream[1]. High-risk cases are streamed to INV while low-risk families can be streamed to the Family Enhancement Program[1]. This article creates a provincial profile of DR streamed investigations while comparing child, household, maltreatment characteristics and case factors associated with each child welfare investigative stream based on the Alberta Incidence Study of Reported Child Abuse and Neglect 2008 (AIS-2008)[6].

Methods

This analysis is based on secondary analysis of the AIS-2008 dataset. The AIS-2008 is the second cycle of a provincial study that examines incidences of reported child abuse and neglect in Alberta for children 17 years and younger. This paper reports on findings based on a total weighted number of 26,957 child investigations that were

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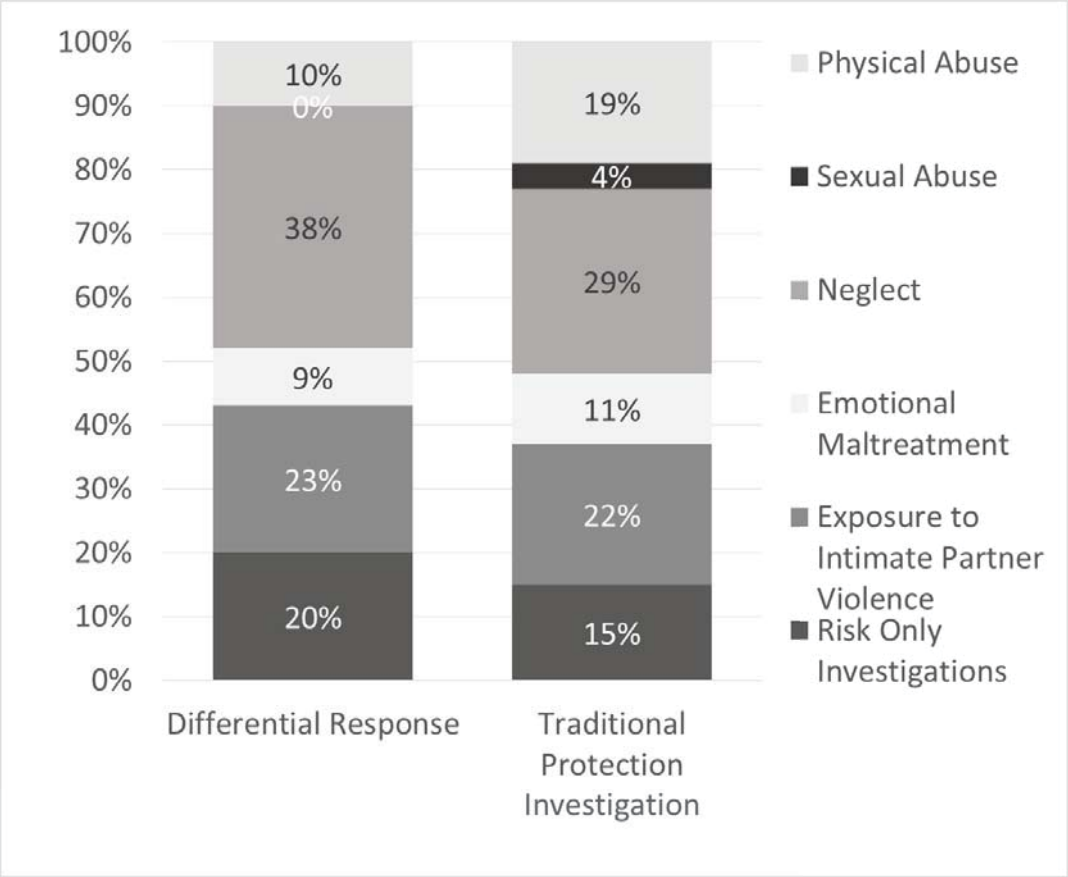

Figure 1:
Primary Categories of All Reported Child Maltreatment Incidents and Risk Investigations in Alberta in 2008 by Child Welfare Investigation Streams. Percentages of type of maltreatment includes total number of child investigations (n=26,957) streamed to differential response (n=6,666), and traditional protection investigation (n=20,291).

noted as either DR streamed investigations, or INV streamed investigations. A total of 6,666 child investigations noted use of DR model, while an additional 20,291 child investigations noted use of INV model. Select comparisons of child, household, case and maltreatment factors from two child welfare investigation streams are presented in this analysis. Bivariate analyses and Pearsons chi-squared test were used to compare each investigative stream and associated factors. For further information on methodology of the AIS-2008 refer to Chapter 2 of the full report [7].

Results

Figure 1 shows primary categories of all reported child maltreatment incidents and risk investigations streamed to DR and INV. Significant differences in child investigations were noted for children younger than 1 year old. Eleven percent of DR streamed investigations involved children who were less than 1 year old, and 8% of INV streamed investigations. Caseworkers were asked to report on nine caregiver risk factors, such as alcohol and/or drug abuse, cognitive impairment, and/or victim of intimate partner violence (IPV) [7]. There were no differences between the two investigative streams for caregiver risk factors.

A risk investigation refers to situations where a specific incident of maltreatment has not yet occurred, however circumstances indicate that there is a significant future risk of maltreatment [7]. DR child investigations more frequently noted risk investigations than INV child investigations. For DR investigations, neglect was noted most

frequently (38%), followed by exposure to intimate partner violence (23%), physical abuse (10%), and emotional maltreatment (9%). Ten percent of DR investigations noted emotional harm requiring treatment, compared to 16% of INV investigations. One percent of DR investigations noted physical harm severe enough to require medical attention, and 2% of INV investigations. The percentage of DR child investigations resulting in a formal child welfare placement was significantly less (5%) than INV child investigations (10%). Twenty-five percent of DR investigations remained open for ongoing services compared to 32% of INV investigations. DR investigations less often resulted in an application to child welfare court (4%), than INV streamed investigations (13%).

Discussion

This secondary data analysis examined 26,957 child maltreatment investigations from the AIS-2008 dataset. The purpose of this exploratory analysis was to provide a provincial profile of families who experience DR child maltreatment investigations, and INV child maltreatment investigations. DR investigations noted less harm, and severity than INV investigation, and more often resulted in less intrusive outcomes. DR investigations had lower percentages of outcome factors including out of home placement, ongoing service provision, and child welfare court applications for lower risk cases that would have otherwise been subject to INV approach. The availability of this alternative approach to investigations allows child welfare workers to provide a stream lined investigative stream that best meets the needs of families. Future research should examine long term outcomes of investigations streamed to DR and INV. Exploring long term outcomes will provide greater insight into the effectiveness of DR model child maltreatment investigations.

Limitations

While the AIS-2008 dataset provides a unique opportunity to examine the child welfare response to reported maltreatment in Alberta, a number of considerations for this secondary analysis must be made when interpreting these findings. The AIS-2008 dataset; 1) only tracked reports investigated by child intervention services and did not include reports that were screened out, only investigated by police, and never reported; 2) is based on the assessments provided by the investigating child intervention workers and could not be independently verified; 3) is weighted using annual estimates which included counts of children investigated more than once during the year, therefore the unit of analysis for the weighted estimates was a child investigation; 4) as weighted estimates provided some instances where sample sizes were too small to derive publishable estimates[7].

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Feature Article Part 2:
A Comparision of Two Cohorts Among Child Welfare Investigations in Alberta: Child, Caregivers, Household, & Case Risk Factors

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Introduction

In 2008, the province of Alberta reported children eleven years and younger made up 71% of all child maltreatment investigations[5]. More than 8,400 children five years of age or younger came to the attention of child welfare in Alberta in 2008 for allegations of child abuse and neglect, compared to approximately 7,700 children ages six to eleven years of age.

Younger children (ages 11 years and younger) are especially vulnerable to their surrounding environments and are heavily dependent on their caregivers to meet basic needs; which inevitably provides the foundation for their future developmental growth[6]. It is imperative for younger children to achieve critical developmental milestones such as language, brain development, emotional regulation, and attachment bonds as these milestones heavily impact later life outcomes[6]. Studies indicate that younger children who experience maltreatment have an increased risk for health, behavior, and psychological issues later in life[2,5,6], which contributes to increased risk of depression, poorer academic performance, and higher levels of aggression in later childhood and adolescent years[1,3,6,8,9]. Examining child, caregiver, household, and case risk factors of reported child maltreatment investigations associated with children 0 to 5 years old and children 6 to 11 years old will contribute to a greater understanding of the complex experiences between these child age groups. This paper seeks to provide researchers and practitioners with awareness concerning the impact of risk factors concerning these populations.

Methods

This secondary analysis was conducted on data collected for the Alberta Incidence Study of Reported Child Abuse and Neglect (AIS-2008). The AIS-2008 collected 2,239 child maltreatment investigations from fourteen randomly selected child intervention services offices over a three month case selection period (October 1, 2008 to December 31, 2008). Offices were stratified by jurisdiction and size to ensure that all subpopulations were fairly represented in the study, with additional consideration for Aboriginal organizations. Select comparisons of child, family,

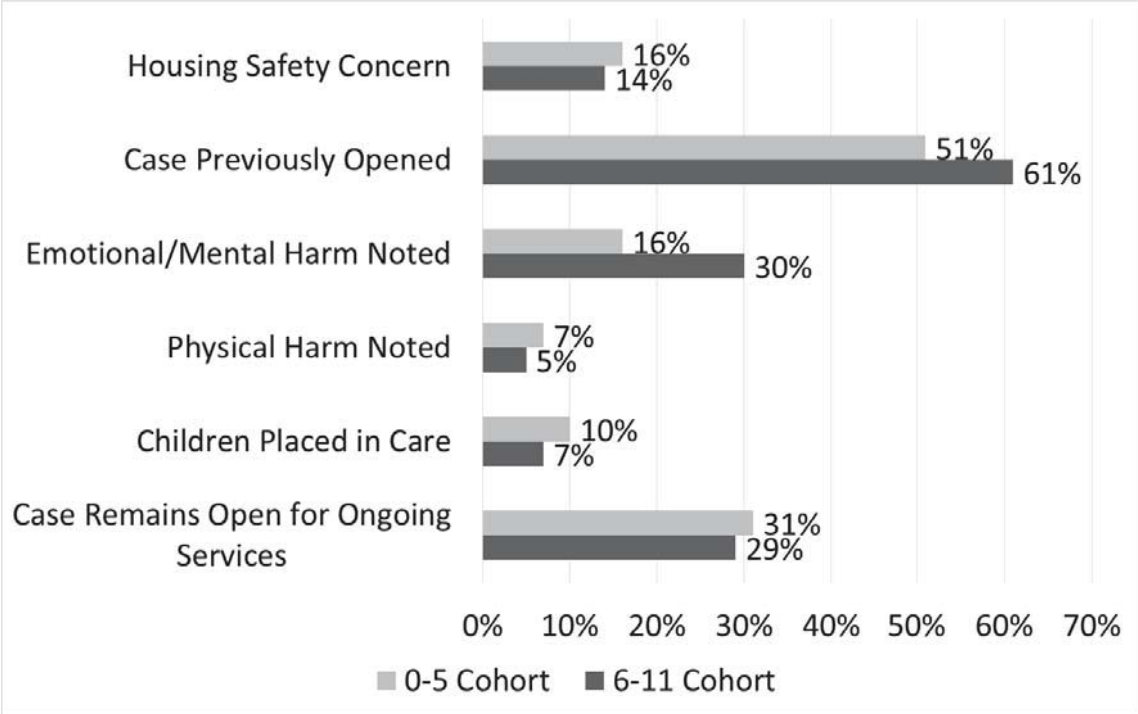

Figure 1:
Percentages of case characteristics include all child investigations for incidents of child maltreatment where a child 11 years or younger was involved (n=16,120), 0-5 years old cohort (n=8,415), and 6-11 years old cohort (n=7,705).

household, and case factors of child maltreatment investigations and risk of future maltreatment investigations are presented below. The analyses compares two child age cohorts: 0-5 years old and 6-11 years old. Bivariate analyses and Pearsons chi-squared tests were used to examine differences in risk factors associated with the younger and older cohorts.

This analysis was conducted using weighted estimates of 16,120 child investigations for incidents of maltreatment involving children 11 years of age and younger in Alberta. Of the total weighted estimate, 8,415 alleged child maltreatment investigations involved children five years and younger and 7,705 maltreatment investigations involved children between six and 11 years of age. Analysis included substantiated, suspected and unfounded investigations for the two cohorts from the AIS-2008 data. For further information, refer to the methodology chapter of the AIS-2008: Major Findings Report[5].

Results

Figure 1 shows case risk factors for child investigations where a child 11 years old and younger was involved. Thirty-one percent of the 0-5 year old cohort remained open for on-going services and 9% of cases were streamed to differential or alternative response. Twenty-nine percent of the 6-11 cohort remained open for on-going services and of those, 10% of cases were streamed to differential or alternative response. Fifty-one percent of investigations of the 0-5 cohort were previously reported to child welfare for suspected maltreatment. For the older cohort, 61% of investigations were previously reported to child welfare for suspected maltreatment.

Workers were asked to report on 6 housing safety concerns: accessible weapons, accessible drugs or drug paraphernalia, drug production or trafficking in the home, chemicals or solvents used in production, other home injury and health hazards. One or two of these household hazard risk factors were identified in 16% of investigations in the 0-5 cohort and 14% in the 6-11 cohort. For the 0-5 cohort, emotional harm

was documented in 16% of investigations, whereas physical harm was noted in 7% of investigations. For the older cohort, emotional harm was documented in 30% of investigations and physical harm was documented in 5% of investigations. While 10% of the 0-5 cohort investigations were placed in a child welfare placement, 7% of 6-11 cohort investigations were placed in a child welfare placement.

Discussion

This secondary analysis of the AIS-2008 dataset examined child, caregiver, household, and case risk factors associated with the two youngest cohorts investigated by the child protection system. Findings from this analysis show increased percentages of multiple risk factors for children 0 to 5 years old, supporting the need to focus on both the additive effects and breadth of risk factors pertaining to child investigations, rather than focusing on solely one risk factor during an investigation. The present findings indicate that families with young children in the child welfare system are faced with many risk factors (parental mental health, social isolation, drug or alcohol abuse, intimate partner violence, financial hardship) and may also have young children performing poorly in multiple areas of development. The array of risk factors and protective factors (child characteristics, household risk factors, caregiver risk factors, and case characteristics) identified by child welfare workers could potentially shape prevention and intervention strategies in preventing rates of re-referral and increase overall positive outcomes for children and families.

Limitations

While the AIS-2008 dataset provides a unique opportunity to examine the child welfare response to reported maltreatment in Alberta, a number of considerations for this secondary analysis must be made when interpreting these findings. The AIS-2008 dataset; 1) only tracked reports investigated by child intervention services and did not include reports that were screened out, only investigated by police, and never reported; 2) is based on the assessments provided by the investigating child intervention workers and could not be independently verified; 3) is weighted using annual estimates which included counts of children investigated more than once during the year, therefore the unit of analysis for the weighted estimates was a child investigation; 4) as weighted estimates provided some instances where sample sizes were too small to derive publishable estimates[5].

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Feature Article Part 3: Associated Factors of Investigations Involving Intimate Partner Violence and Other Forms Of Maltreatment: Child, Family, Household, and Case Characteristics

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Introduction

Intimate partner violence is noted in a child maltreatment investigation when a child is exposed to an incidence of verbal or physical aggression between 2 or more adults in the home[3]. The co-occurrence of intimate partner violence (IPV) and child maltreatment intensifies the trauma experienced by children, compared with children who experience IPV alone[3]. IPV is linked to many negative developmental outcomes[2,7]. Children exposed to IPV are at risk for more social challenges[8], emotional issues[1,8], attachment issues[3], behavioural disorders [3], and academic challenges[3,8]. Some researchers state that the involvement of child welfare services in matters related to IPV result in overly intrusive interventions, such as the removal of a child from their home, or increased involvement with child welfare services. Other research suggests that children exposed to IPV alone do not receive more intrusive intervention, but require comparable support as children experiencing other forms of maltreatment[2,4,6] .

The Alberta Incidence Study of Reported Child Abuse and Neglect 2008 (AIS-2008) is a provincial study examining the characteristics of reported child abuse and neglect[5]. The AIS-2008 dataset provides the opportunity to examine characteristics of children and families involved in IPV child investigations, as well as the short term outcomes. This analysis examines evidence supporting or challenging the use of child welfare services for children and families experiencing IPV in Alberta in 2008.

Methods

The AIS-2008 is the second provincial study on child abuse and neglect to be conducted in Alberta for children 17 years and younger[5]. This article presents select comparisons of child, family, household and case factors across 3 groups of substantiated child

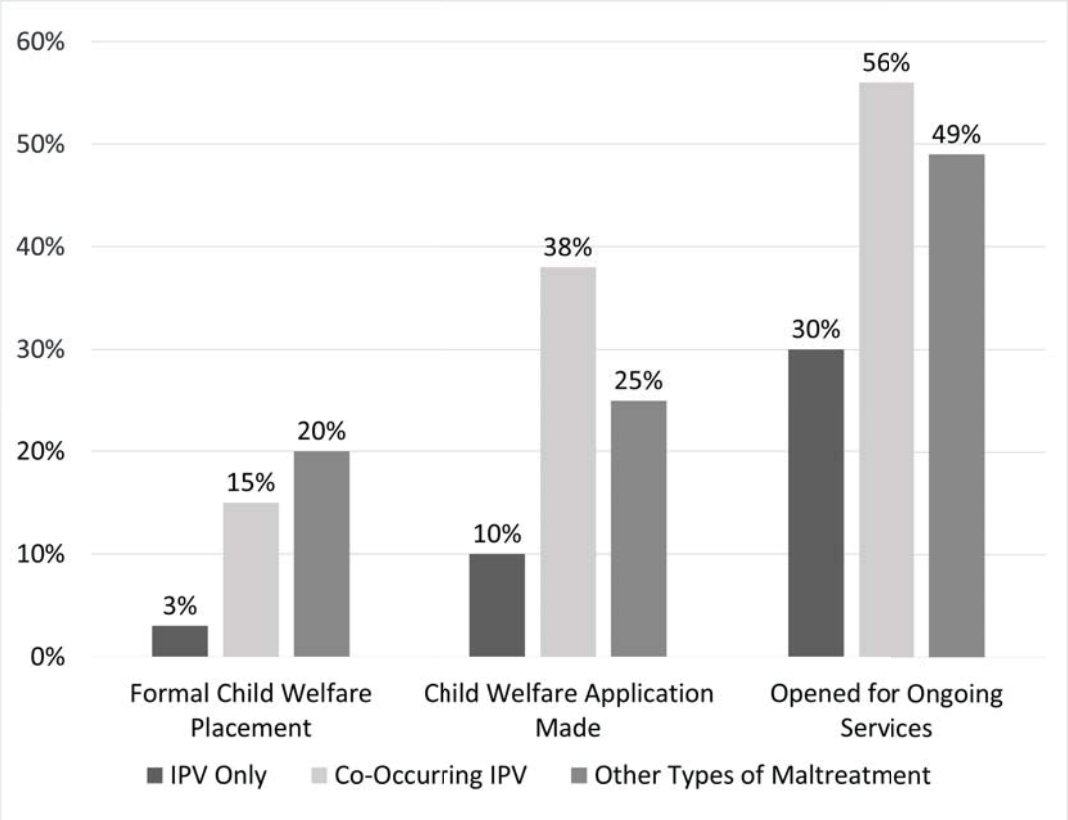

Figure 1:
Percentages of case characteristics include 14,404 child maltreatment substantiated investigations. This includes 3,898 IPV only investigations (27%), 2,302 co-occurring investigations (16%), and 8,204 other forms of maltreatment investigations (57%).

investigations. This includes: 1) IPV only child investigations where IPV was noted as the single child maltreatment concern; 2) co-occurring child investigations where IPV and at least one other form of child maltreatment (physical abuse, sexual abuse, neglect and emotional maltreatment) was noted; and 3) other forms of maltreatment child investigations involving other forms of child maltreatment excluding concerns of IPV. Child welfare services define IPV as a form of maltreatment if a child had allegedly been a direct witness to physical violence, had indirect exposure to physical violence, and/or exposure to emotional violence (including verbal abuse). The analyses presented in this article are based on annual and regionally weighted estimates of substantiated child investigations examining a total of 14,404 substantiated child maltreatment investigations. This includes 3,898 IPV only investigations (27%), 2,302 co-occurring investigations (16%), and 8,204 other forms of maltreatment investigations (57%). Bivariate analyses and Pearsons chi-squared tests were used to compare IPV investigations with co-occurring investigations and other forms of maltreatment investigations. For further information on the methodology of the AIS-2008 refer to Chapter 2 of the full report [5].

Results

Child welfare workers were asked to report on 9 caregiver risk factors at the time of the investigation. Victim and/or perpetrator of domestic violence was excluded as a household caregiver risk factor. Caregiver risk factors varied considerably between IPV only investigations, co-occurring investigations, and other forms of maltreatment investigations. For IPV only investigations, this included alcohol abuse (58%), few social supports (49%), and mental health

issues (35%). For co-occurring investigations, alcohol abuse (79%), mental health issues (56%), and few social supports (54%) were the top three concerns that were noted. Other forms of maltreatment investigations identified few social supports (45%), mental health issues (41%), and alcohol abuse (34%).

The level of harm was significantly lower for IPV only investigations than both co-occurring investigations and other forms of maltreatment investigations as observed in the following factors. Fifteen percent of IPV investigations noted severity of emotional harm requiring treatment, compared with 39% of co-occurring investigations, and 26% of other forms of maltreatment investigations. Estimates of severity of physical harm were too low to report for IPV only investigations. Sixty-six percent of IPV only investigations involved multiple maltreatment incidents, 88% in co-occurring investigations, and 70% in other forms of maltreatment investigations. Child investigations resulting in out-of-home placement greatly varied by each comparison group. Three percent of IPV only investigations noted formal child welfare placement, 15% in co-occurring investigations, and 20% in other forms of maltreatment investigations. Workers referred 30% of IPV only investigations to ongoing services compared to 56% of co-occurring, and 49% of other forms of maltreatment.

Discussion

The AIS-2008 dataset provides child, caregiver, household, and case factors associated with IPV only investigations, co-occurring investigations, and other forms of maltreatment investigations. While there is concern that the involvement of child welfare in IPV investigations will result in more intrusive interventions [6], findings from this analysis support Black et al. (2008)[1] who recognized that IPV as a single concern does not necessarily result in more intrusive outcomes. Co-occurring investigations noted the highest severity of harm, compared to IPV only investigations and other forms of maltreatment investigations. Subsequent analyses will build on this work in order to examine specific risk and protective factors that are predictive of child welfare placement and the provision of ongoing services.

Limitations

While the AIS-2008 dataset provides a unique opportunity to examine the child welfare response to reported maltreatment in Alberta, a number of considerations for this secondary analysis must be made when interpreting these findings. The AIS-2008 dataset; 1) only tracked reports investigated by child welfare services and did not include reports that were screened out, only investigated by police, and never reported; 2) is based on the assessments provided by the investigating child intervention workers and could not be independently verified; 3) is weighted using annual estimates which included counts of children investigated more than once during the year, therefore the unit of analysis for the weighted estimates was a child investigation; 4) as weighted estimates provided some instances where sample sizes were too small to derive publishable estimates[5].

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Southern Alberta Vasculitis Patient Registry: Creation And Utility

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Vasculitides encompass a group of rare autoimmune diseases where inflammation of vessels causes multisystem organ damage (i.e. kidneys, lungs, nervous system, Figure 1). The overall incidence is currently estimated to be 10-20/million/year, however there is an increasing trend noted in the pediatric population in Alberta[1,2].

As with other rare autoimmune diseases such as lupus, the limited number of patients impairs recruitment into clinical trials, impedes research, and hinders the generation of evidence-based treatment recommendations and protocols[4]. Moreover, the low patient numbers provide a barrier to obtaining reliable rare disease prevalence statistics and to gaining a clear understanding of the natural history of specific vasculitides.

To address some of these limitations, we propose to generate a prospective vasculitis registry for patients in Southern Alberta. This initial registry will serve as a foundation for collaboration with other established or prospective centres at the provincial, national, and international levels (Figure 2). The contribution of Canadian centres is coordinated through the Canadian network for research on vasculitides (CanVasc), representing a network of physicians with expertise in vasculitis. To ensure the seamless amalgamation of information among the centres, the same nomenclature and database platform will be used by each provincial vasculitis centre. The establishment of such a registry will create a framework for knowledge translation, discovery, and best practice management.

Methods

Recruitment will initially be limited to patients with vasculitis residing in Southern Alberta who have been referred to the Rheumatology division in Calgary through the central triage system to ensure capture of patients with a confirmed diagnosis. Ethics approval for this research project was obtained in May 2012. Patients complete written informed consent at their baseline visit in the Rheumatology vasculitis clinic at the South Health Campus in Calgary, Alberta. Upon consenting, the patients are examined yearly by Dr. Aurore Fifi-Mah, a Rheumatologist at the South Health Campus. The research team will complete yearly case report forms where information on patient symptoms, test results, response to treatment, activity of disease and complications will be longitudinally collected. Each patient will also complete a Patient Quality of Life form (SF-36).

Patient consent also extends to the collection of de-identified sera for storage in the Mitogen Advanced Diagnostics Laboratory in Calgary, Alberta, under the direction of Dr. Fritzler. As new diagnostic and prognostic biomarkers are identified, these sera will constitute a biobank to be analyzed for the presence of new target antibodies and proteins. Such information can enhance understanding of the pathogenesis of these diseases to inform and direct future therapeutic approaches. Biomarkers could also help with early

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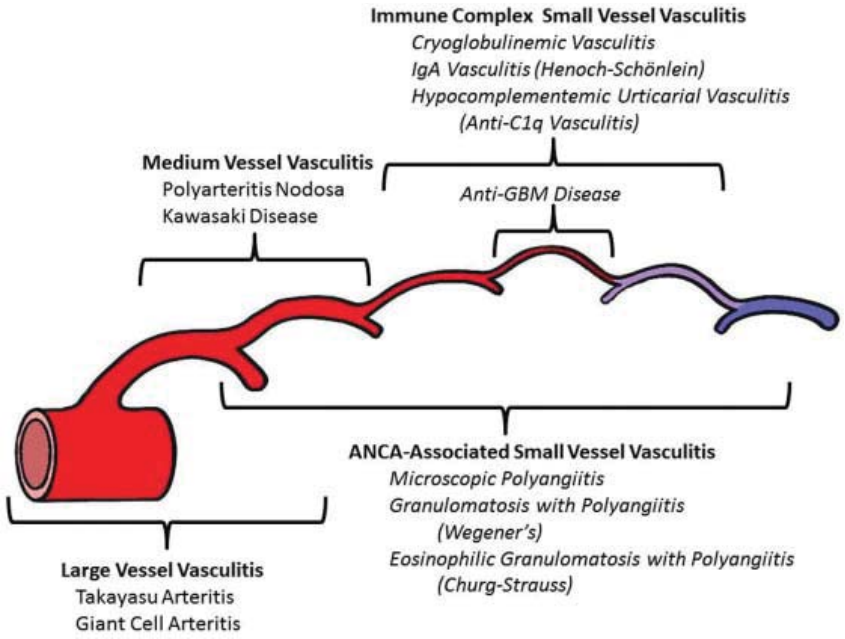

Figure 1:
The 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides[3].

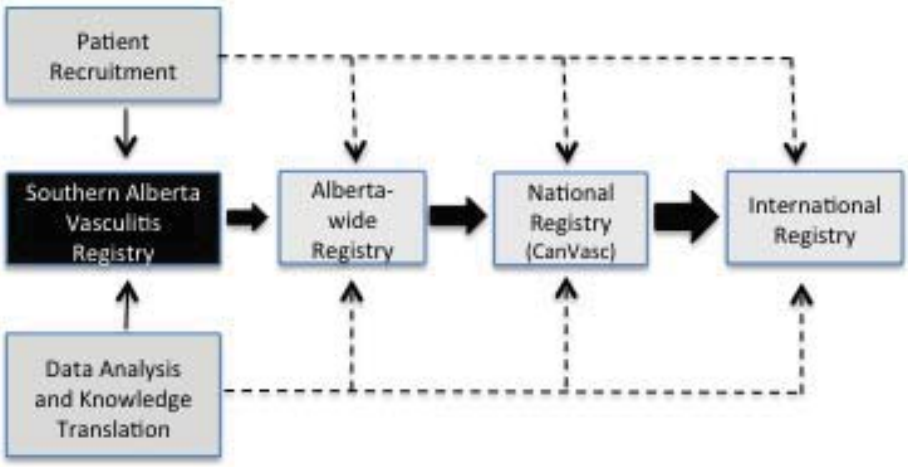

Figure 2:
Schematic of expansion of the Southern Alberta Vasculitis Registry. (CanVasc: Canadian network for research on vasculitides; http://www.canvasc.ca)

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Table 1: *Current numbers and proportions of patients categorized by specific vasculitides in the Southern Alberta Vasculitis Patient Registry.*

Diagnosis	Number	Percentage
ANCA-associated Vasculitis	12	11.2
Behçets Disease	7	6.5
Connective Tissue Disease Associated Vasculitis	6	5.6
Central Nervous System Vasculitis	4	3.7
Cryoglobulinemic Vasculitis	2	1.8
Giant Cell Arteritis	9	8.4
IgA Vasculitis	5	4.6
Leukocytoclastic Vasculitis	11	10.2
Polyarteritis Nodosa	11	10.2
Polymyalgia Rheumatica	13	12.1
Takayasus Arteritis	6	5.6
Vasculitis Associated with Other Disease	22	20.5

detection of disease relapse to reduce permanent organ damage and improve prognosis.

As this is an observational study, no power calculation is involved. Descriptive analysis will be used to summarize participant characteristics and comorbid conditions.

Results

The initial project infrastructure has been successfully established. To date, 107 patients have been recruited (Table 1).

Discussion and Conclusions

The establishment of a Southern Alberta Vasculitis Patient Registry allows the development of a prospective cohort of patients with vasculitis seen in Calgary, the catchment area for Southern Alberta. The data collected include clinical and serological information that will be captured in a database. The development of a biobank of sera with access to an internationally recognized immunology laboratory in Calgary will provide the basic science and technical support to improve diagnosis and management of patients based on their biomarker profile. This will help address issues of inaccurate rare disease statistics, inadequate understanding of disease natural history, and limited diagnostic and treatment regimes. Through systematic collection and analysis of data, the registry will create a foundation of knowledge on which to build informed, standardized models of care by identifying gaps in patient care.

Moreover, the additional benefit of serum analysis may permit the discovery of specific biomarkers and prognostic factors to classify and predict the future course of different vasculitis subtypes. This will permit individualized, patient-centred treatment.

The extension of this project to include centres provincially, nationally, and internationally would magnify the utility of the initial project. The previous establishment of provincially-based vasculitis research centres through CanVasc expedites project expansion.

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Predicting the Mortality of Pneumonia-Induced Direct Lung Injury Using Serum Metabolomics

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Acute respiratory distress syndrome (ARDS) has significant impact on the morbidity and mortality in the intensive care unit. It is estimated that there are 86.2 cases of ARDS per 100,000 people. This disease has an average mortality rate of approximately 38.5%[1]. Severe ARDS has a 49% mortality rate, with mortality increasing with age[1]. Currently, there are no viable specific treatment options in the intensive care unit for ARDS other than non-specific supportive care. As such, the purpose of this study was to use serum metabolomics to further characterize the mortality of patients with pneumonia-induced ARDS in the intensive care units at the Peter Lougheed Center, and the Foothills Medical Centre in Calgary, Alberta, Canada. It was hypothesized that using serum metabolomics would more accurately predict outcome in pneumonia-induced ARDS when compared to current used predictive indexes such as APACHE II or lung injury score.

The diagnostic criteria for ARDS include the acute onset of non-cardiogenic pulmonary edema, hypoxia, and presence of bilateral pulmonary infiltrates)[2]. Moreover, the state of patient hypoxemia and the fraction of inspired oxygen can be used to calculate a ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen ratio (PaO_2/FiO_2 ratio). The ratio varies decreasing from in the 500s to less than 100, with a healthier lung having higher PaO_2/FiO_2 ratio. The specific PaO_2/FiO_2 ratio were used to clinically differentiate the severity of lung injury. The Berlin definition of ARDS is used to define the cohorts in this study[3]. Mild, moderate, and severe ARDS are described with PaO_2/FiO_2 ratios of 201-300, 101-200, and ≤ 100, respectively.

Metabolomics analysis is a systems-biology approach used to identify metabolites of organisms such as humans and plants[4]. This can be done by analyzing multiple biofluids (e.g. serum, plasma, urine) and utilizes spectroscopic methods such as proton nuclear magnetic resonance (^{1}H-NMR), gas chromatography mass spectrometry (GC-MS), and liquid chromatography mass spectrometry (LC-MS)[5]. In this study, we used ^{1}H-NMR.

Metabolomic profiling was completed to see if metabolomic fingerprints (biomarkers) can predict ICU outcome (death) in pneumonia-induced acute respiratory distress syndrome (ARDS).

Methods

Patient Selection

The selected population in the study consisted of adults admitted to the intensive care units at the

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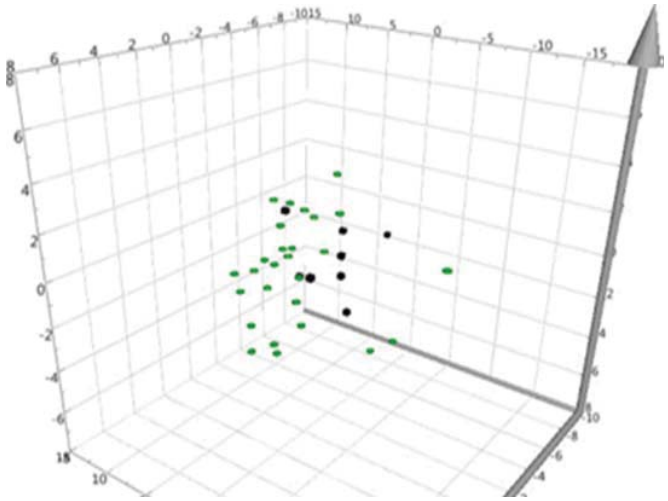

Figure 1:
PCA model of mild and severe pneumonia-induced ARDS. Model is based on 28 day mortality, and shows significant clustering between alive and dead outcomes. (27 alive, 8 dead, R^2Y=0.562, x-axis: prediction component). Green dots (alive), black dots (dead) at 28 days.

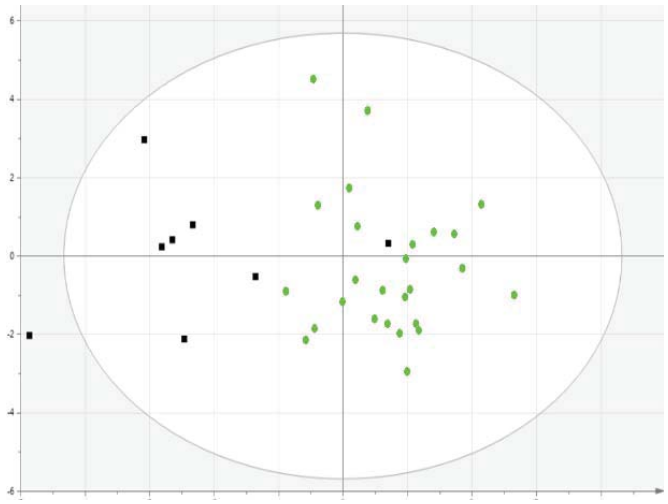

Figure 2:
OPLS-DA plot of mild and severe pneumonia-induced ARDS. Model shows distinct separation between alive and dead outcomes (27 alive, 8 dead, R^2Y=0.61, Q^2Y=0.458, p=0.004, x-axis: prediction component, y-axis: orthogonal component). Green dots (alive), black dots (dead) at 28 days.

Foothills Medical Centre and Peter Lougheed Centre in Calgary, Alberta, Canada with pneumonia-induced direct lung injury between 2009 and 2014. Blood was drawn from these patients on day 1 of ICU stay. Of the 868 adult patients enrolled in the Critical Care Epidemiologic and Biologic Tissue Resource (CCEPTR) a total of 97 patients were selected to be enrolled in the study. By applying the specific inclusion and exclusion criteria, patients were grouped into two groups based on severity of ARDS and age- and sex-matched to minimize variable confounders: Mild ARDS (n=18), Severe ARDS (n=18) using the Berlin definition of ARDS.

REDCap Initialization and Data Entry

Upon selection of the 97 patients into their respective cohorts a REDCap (Research Electronic Data

Capture) epidemiologic relational database was used to enter patient data.

Sample Preparation NMR Analysis

Each of the 54 serum samples (200 μl) were defrosted from -80°C to 4°C. 3 kDa NanoSep microcentrifuge filters were prewashed five times with ddH2O, reducing preservative contamination. Then, the samples were filtered via centrifugation at 11963 x g for 1 hour at 4°C using the pre-washed 3 kDa filters. The filtrates were rinsed with 100 μl of D2O. The filtrates were collected into clean 1.5 ml vials. The samples were adjusted to 400 μl with 80 μl of phosphate buffer (0.5 M NaH_2PO_4 buffer solution at pH 7.0) containing 2.5mM 2,2-dimethylsilapentane-5-sulfonate (DSS, final concentration 0.5 mM) as an internal reference compound, 10 l sodium azide (1M NaN_3) to prevent bacterial growth, and D_2O. The pH of the samples was adjusted to 7.0 $\pm$ 0.04 at room temperature. ^{1}H-NMR data for all the samples were generated on a 600 MHz Bruker Ultrashield Plus NMR spectrometer (Bruker BioSPin Ltd., Canada), without bias by the use of an automated sample changer. Bruker 1D proton spectroscopy pre-saturation pulse sequence (noesypr 1d) were used to acquire one dimensional spectra, where an optimal water suppression program and mixing time of 100 ms were used. ^{1}H-NMR spectra were analyzed using the ChenomX NMR Suite 7.1 software (Chenomx Inc., Edmonton, Alberta, Canada) for metabolite identification and quantification using the targeted profiling approach in the profiler module.

Results

The unsupervised PCA model showed significant clustering in the 3-dimensional model for alive- and dead- outcomes for the patients in the study (Figure 1). Eight patients with a dead outcome were clustered together, and denoted by black squares (Figure 1). The patients with an alive outcome showed clustering in their respective coordinates, and were represented by green squares (Figure 1). 2 and 3-dimensional OPLS-DA models were generate and revealed statistically significant separation for predicting the alive and dead outcomes for the patient cohort on day one of OCU admission. As the black squares (dead) and green squares (alive) are positioned on separate portions of the orthogonal component (x-axis), a separation is observed between the two states (Figure 2).

Discussion and Conclusions

The purpose of this study was to determine if there was a statistically significant metabolomics difference in 28-day mortality for patients with ARDS. The use of ^{1}H-NMR to establish a metabolic distinction in ICU outcome (dead or alive) for patients with pneumonia-induced ARDS was needed ICU stay. This study was successful in determining a model to separate 28 day mortality in mild vs severe pneumonia- induced ARDS patients from samples taken on the first day of ICU admission.

An unsupervised PCA model of the 55 metabolites detected by ^{1}H-NMR dataset was based on 28 day mortality for patients with pneumonia-induced ARDS. The PCA plot revealed statistically significant data clustering between groups, demonstrating that alive patient outcome can be separated from the dead outcome (Figure 1). In the OPLS-DA model, significant and predictive separations were observed in the alive and dead outcomes (Figures 1, 2). R^2Y values measure the differences within the group, and typically give the degree of variation explained by the model. The R^2Y value determined from the OPLS-DA plot was 0.61, suggesting reliable statistical variation in the data. The OPLS-DA model revealed a Q^2Y= 0.458 and p-value of 0.004. The Q^2Y is a measure of model predictability and this value suggests good predictability of ICU outcome. An excellent separation between the serum profile for the alive and dead outcomes in pneumonia-induced ARDS patients was observed.

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Aging is Associated with Reductions in Fascicle Length, Sarcomere Length and Serial Sarcomeres

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Aging is associated with muscle weakness and decreased muscle performance due, in part, to impaired active force production. Aging also affects the muscles passive force properties, but in the opposite manner. Passive muscle force in old age has been shown to be elevated above that of young, which may be related to increased muscle stiffness with age. The purpose of this study was to investigate age related sarcomere length, sarcomere number and fascicle length changes that may contribute to increased passive force. It was hypothesized that fascicle length in old age would be shorter compared with young, however, the sarcomere length would remain unaltered. The muscle length where peak force occurred (L_o) was determined for the medial gastrocnemius muscle (MG) of young (n = 9) and old (n = 8) rats. The MG was fixed at Lo in 10% formalin, digested in nitric acid and individual fascicles were isolated. Fascicle length, sarcomere number and the sarcomere length were then compared at Lo. In comparison to the MG of young rats, old rats showed a reduction of 14% in fascicle length, 4% in sarcomere length and 10% in sarcomere number, (P ¡ 0.05).Shorter fascicle lengths and reduced sarcomeres in series in the MG from old rats may explain increased passive forces in older individuals. Reduced sarcomere number in series would lead to overstretched sarcomeres, leading to increased tension on sarcomere passive force structures and sarcomeres operating on the descending limb of force-length relationship.
Keywords: passive force, skeletal muscle, rat, laser diffraction, medial gastrocnemius.

Introduction

With natural human aging, there is a loss of muscle mass and alterations to the structural components of the human muscular system that results in impaired contractile function and performance[1,2]. Muscle weakness associated with old age contributes to declines in muscular function and is associated with impairments in activities of daily living[3]. On the other hand, older adults maintain force production during lenthening contractions (i.e. eccentric contraction) relative to other contraction modes[1]. The age-related maintenance of eccentric strength is evident in whole muscle and skinned single fibre preparations[1]. In addition to many of the mechanisms proposed for the preservation of eccentric strength, alterations to the structural properties of the muscle fascicle leading to elevated passive force have not been investigated[4,5]. A potential unexplored mechanism

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for increased passive force in old age could be decreased muscle fascicle lengths owing to either a decrease in the number of sarcomeres in series and differences in sarcomere length[6]. Thus the fascicles and sarcomeres of muscles from old and young rats may experience divergent length changes for a given displacement or joint angular rotation, resulting in increased stiffness in the aged muscles. The purpose of this study was to compare the medial gastrocnemius of young and old rats to determine fascicle length, serial sarcomere numbers and the sarcomere length at which peak force is obtained (i.e. plateau of the force-length relationship; L_o) It was hypothesized that fascicle length in old rats would be shorter compared with young owing to lesser sarcomeres in series, however, the sarcomere length at Lo in old rats will remain unaltered as compared with young.

Methods

Two groups of Fisher344 x Brown Norway hybrid rats (n = 17) were used in this experiment, a young cohort (7-8 months 20 human years) (n = 9) and very old cohort (30-35 months; 75-80 human years) (n = 8). The MG from the right leg was surgically isolated, attached to a custom made muscle puller and force transducer. For whole muscle activation, the tibial nerve was isolated and electrically stimulated via a nerve cuff. The L_o was determined by performing a standard force-length relationship. Contractions were evoked at 200 Hz of 250 ms duration separated by 2 min rest across 1 mm increments from -4 mm to +4 mm starting at a baseline length near zero force. The animals were then sacrificed and the hind limb was immediately placed in a VWR 10% Formalin (fixative) solution at the muscle length corresponding to L_o. After a 1 h period of fixation, the MG muscle was firmly secured to a wooden applicator stick at Lo and allowed to fix for a 2 week period in a VWR 10% Formalin solution. The muscles were then dissected into 4 lengthwise sections medial and lateral of the center of each MG muscle belly. After a 4 hour, 30% nitric acid digestion process, 5 individual fascicles from each muscle section were isolated and placed on slides for sarcomere length measurement at 5 locations along the fascicle by laser diffraction. In this method, the laser beam (1mm wide, λ = 630 nm) penetrated through the thin actin filaments, but not the thick myosin filaments, creating a superposition of gratings of aligned myofibrils[7]. The first order diffraction distance was used to mathematically determine the average sarcomere length in the measured area using the sarcomere length equation (Fig. 1). Sarcomere Length Equation (L_s):

Fascicle length measurements were taken using a Matrox imaging software and camera. Serial sarcomere number was calculated by dividing the fascicle length by the average sarcomere length. In total 20 fascicle length and 100 sarcomere length measurements were obtained from each muscle, which resulted in a total of 340 fascicle length and 1700 sarcomere length measurements. Comparisons between age groups were performed using unpaired bilateral Students t-tests. Unless otherwise specified, all values are reported as mean standard deviation. The level of significance was set at $p<0.05$.

Results

A reduction in muscle fascicle length of 14% was observed in the old rats (average = 11.3 1.0 mm) when compared to young rats (average = 13.1 1.1 mm), $p<0.05$. There was a reduction in average sarcomere length of 4% observed in the old rats (average = 2.22 0.11 m) versus the young rats (average = 2.31 0.05 m), $p<0.05$. The MG of old rats showed 10% fewer sarcomeres in series (average = 5087 465 sarcomeres) when compared to young rats (average = 5684 440 sarcomeres), $p<0.05$ (Fig. 2).

Discussion

The goal of this study was to determine whether there were differences in fascicle length, sarcomere length and sarcomere numbers at Lo in the MG muscle of young and old rats. The muscles from old rats had shorter fascicle lengths owing to less sarcomeres in series, as well as shorter average sarcomere lengths. The shorter average sarcomere lengths found in the old rat MG muscle compared with young were unexpected as the muscle length of each animal was fixed at the unique Lo (Fig. 2). Since sarcomeres have an optimal length for force production based on the overlap of thick (myosin) and thin filaments (actin) and vertebrates exhibit very little range for this

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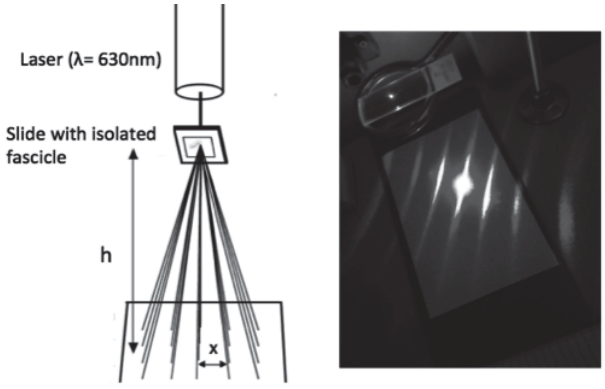

Figure 1:
Laser diffraction experimental setup for sarcomere length measurements. First order diffraction distance indicated by x. Image adapted from Science and Engineering Education, University of Wisconsin, 2008, http://education.mrsec.wisc.edu/supplies/OTK/index.html.

optimal sarcomere length, no change was expected in sarcomere length[5]. One possible explanation for the shorter sarcomeres at Lo could be related to a reduced myosin concentration, which has been reported previously for the soleus muscle of aged rats[8]. Although speculative, the lesser myosin content could shift the sarcomere force length (FL) relationship to shorter lengths to possible increase the availability of cross-bridges and thus maintain for optimal overlap[8]. A second, and perhaps more plausible explanation for the shorter average sarcomere length in old compared with young could be owing to an age-associated shortened actin filament length. Since the thick myosin filament is regulated more stringently and is highly uniform in skeletal muscle compared to the thin actin filament, actin filament lengths could also be altered in old age, leading to shorter sarcomeres[10]. A proposed mechanism of actin length regulation is based on capping proteins, which determines thin filament binding properties and sarcomere length. These capping properties are down regulated with age leading to shortening of the thin filament and ultimately reduced sarcomere length[10,11]. Since peak muscle force is dependent on an optimal overlap of actin and myosin filaments to maximize cross bridge formation, shorter thin (actin) filaments, therefore shorter sarcomeres, would cause L_o to occur at a reduced sarcomere length in old age. Another possible explanation for the shorter sarcomere length in muscle from old rats may be related to a limitation of the study where the L_o was measured at an optimal active contraction, but the muscles were fixed in a passive state. The shorter sarcomeres in old muscle could therefore be due to factors such as the series elastic property differences in young and old muscles, which play a role in passive length. Therefore, when the muscle is no longer actively contracted and enters a passive state, the stiffer series elasticity in old muscle would keep it at a shorter length than the young muscle[12]. Due to this limitation, it was unknown as to whether sarcomere length was altered as it entered the passive state or whether the difference was indeed due to an age related alteration to the sarcomere structure. An important point must be made regarding the range of sarcomere lengths on the plateau of the FL relationship. For rat skeletal muscle, assuming an actin length of 1.13 m and a myosin length of 1.53 m, one would presume maximal force would be obtained at sarcomere lengths between 2.26 m and 2.43 m, which corresponds to the sarcomere length observed in the present study (Fig. 2)[13]. Since, on the force-length curve plateau, there is not a single sarcomere length for maximal force production, but a range of lengths spanning 7% of the force length curve. Therefore, the 4% range in this experiment could be all be found on the plateau region of the sarcomere FL relationship[9]. In line with the hypothesis, the age related reduction in fascicle length of 14% observed in this experiment (Fig. 2) was consistent with previously published findings of a 10-17% reduction in fascicle lengths in humans[2,14] and rats[6]. The reduction in fascicle length was associated with a lower total sarcomere number in series for the old age cohort (Fig. 2). The lower

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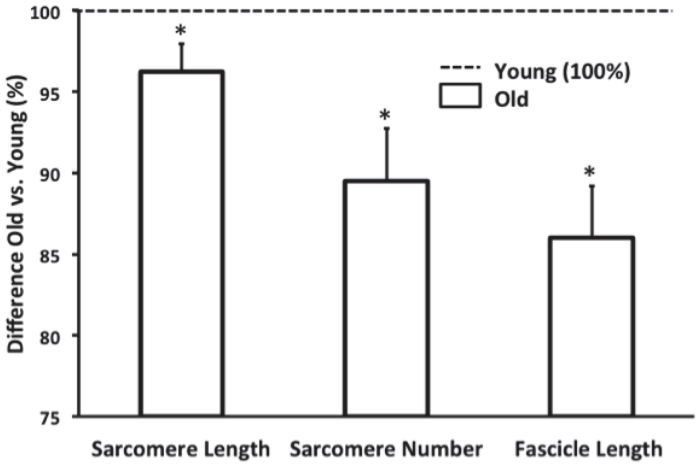

Figure 2:
Percent difference in sarcomere length, sarcomere number and fascicle length from the MG of young rats (100%) vs. old rats measured at Lo. Bars indicate standard error. Significance indicated by * ($p<0.05$).

sarcomere number in the old rats occurred despite shorter sarcomere lengths. Therefore the reduction in fascicle lengths at L_o in the old rats was large enough to reduce serial sarcomere number. Serial sarcomere number is important when considering the sarcomere force length relationship[9]. For example, if the limbs of young and old were at matched joint angles such as occurs in vivo, assuming a given joint angular displacement produces a similar sarcomere excursion across age, the shorter fascicles in the old rats would mean the sarcomeres would be stretched to longer lengths. Based on the sarcomere FL relationship, this would mean at the sarcomere level, older adults may be operating further on the descending limb of the FL relationship thus generating less active force but more passive force ultimately contributing to muscle weakness throughout a functional range of motion. Additionally, during stretch, where aged muscle sarcomeres are being pulled to relatively longer lengths, passive force producing elements such as the giant protein titin may play a larger role in contributing to increased passive tension and the age-related maintenance of eccentric strength in muscles from older adults[1]. Moreover, it has been proposed that increased tendon compliance with old age may have a compensatory effect, where the shorter fascicles and fewer sarcomeres of aged muscle are stretched less. The age-related increase in tendon compliance in older age would assist in maintaining the sarcomere filament overlap to be closer to the optimal force production length[15], this is an area of future investigation.

Conclusion

The results of this study were in accordance with the hypotheses that as individuals age, not only are sarcomeres lost in parallel but are also lost in series, resulting in shorter fascicles. But quite unexpectedly average sarcomere length was shorter at L_o in the old compared with young muscle. The consequences of these age related muscle changes are less functional range of motion for older adults and less force throughout that range of motion to perform the task of daily living. These results may also help to explain the increased passive force of muscles of older individuals.

Acknowledgements

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Effects of Temperature and Angular Velocity on Eccentric Force of an Intrinsic Thumb Muscle

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Temperature and velocity have significant effects on muscle contractile properties. For example, it is well known that changing angular velocity and altering muscle temperature can change the force-producing capacity of muscle. It is typically understood that with increasing shortening velocity and cooler temperature force decreases. However, the influence of temperature and angular velocity on force during lengthening contractions is less understood. The purpose of this study was to determine whether temperature and/or velocity has an effect on the eccentric to isometric force ratio of the adductor pollicis muscle in young males. Ten young (average 25y) male subjects performed lengthening (0-40°) electrically-evoked contractions of the left adductor pollicis muscles at ∼50% of maximum voluntary force at angular velocities ranging from 0-320°/s. This procedure was performed initially at room temperature (21°C), and then repeated two more times after a 20min bath, first in a cold (15°C) water and then in a warm (43°C) water bath in order to change the muscle temperature. The eccentric to isometric ratio was significantly greater in the cold compared to the normal condition (P>0.05), but was not different from normal for the warm condition (P>0.05). The eccentric to isometric ratio was significantly greater at 80, 160 and 320°/s (P<0.05) than at 20/s, but was not different at velocities slower than 80°/s (P>0.05). Instantaneous stiffness was measured 1 s after attaining maximum stretch. There was a significant ∼38% increase in active stiffness in the cold muscle compared to normal. No significant difference (∼15%) in stiffness was observed for the warm compared with the normal condition, and no significant difference (∼20%) was found between warm and cold muscles. The findings suggest that there is an increased force per cross-bridge as temperature approaches normal physiological temperature, but decreases when temperature deviates from normal. **Keywords:** Electrical Stimulation, Eccentric to Isometric Force Ratio, Adductor Pollicis.

Introduction

Eccentric contractions (i.e., active muscle lengthening whereby the external load is greater than the tension produced by the muscle) are a part of everyday life from walking down the stairs to taking a seat in a chair. Eccentric contractions are notable in that they

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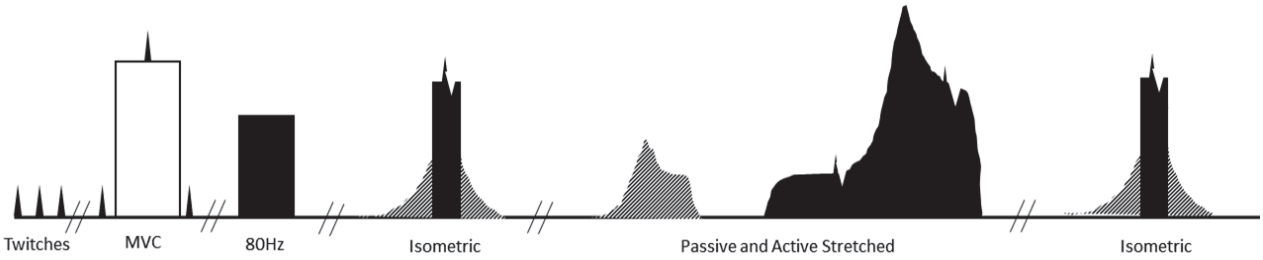

Figure 1:
Experimental Timeline. Contractions conducted within one temperature condition (normal, cold and warm). Open regions are voluntary contractions, grey regions are passive stretches and black regions are electrical stimulation.

have a greater force-producing capacity than purely isometric contractions. Previous work has used the eccentric to isometric force ratio to better understand the properties pertaining to eccentric muscle strength [1]. Stiffness (i.e., increase in force during a fast stretch of a small amplitude) has also been utilized to study the eccentric portion of muscle contractions which can be used to show the approximate proportion of attached cross bridges[2]. However, results with regards to the proportion of attached cross-bridges across temperatures is in contention. For example, Piazzesi et al.[3] found no difference in stiffness across a variety of muscle temperatures, while Lee & Herzog[4] found that the stiffness in single fibres of frog muscles decreases with temperature. Based on the Lee & Herzog[4] study, there was a lack of change in the force seen in the warm compared to the cold muscle. Yet the decrease in stiffness in the warm condition would typically indicate a decrease in force generation. They[4] proposed that this was the result of an increase in the average force produced by each individual cross-bridge via the shifting of the proportion of attached cross-bridges to the strongly bound state.

Within the muscle there is an equilibrium ratio of weakly bound and strongly bound cross-bridge states[5]. The strongly bound are the force producing states, while both the weakly and strongly bound states contribute to stiffness[6]. Cold muscles typically produce less force than warm muscles, with a lack of temperature dependence around 25C in mammalian muscle[7], but may have a similar stiffness, which could be explained by a greater ratio of weakly to strongly bound cross-bridges[5], and a similar proportion of attached cross-bridges in all states[8]. Most studies on temperature effects have been performed in isolated muscle or fibre preparations[5], and little is known about the behavior of muscles in vivo.

Muscle stretch velocity also plays an important role in the force produced in eccentric contractions[9]. For example, the eccentric to isometric force ratio increases with velocity in adult men[10]. However, it is not known if temperature has an influence on the increasing ratio with increasing velocity. The combination of eccentric velocity and muscle temperature on eccentric force production in an adult population has not been fully investigated.

The purpose of this study was to determine whether increasing or decreasing muscle temperature has an effect on the eccentric to isometric force ratio and muscle stiffness in vivo. It was hypothesized that cooling muscles would result in an increase in the eccentric to isometric force ratio due to an increased ratio of weakly to strongly bound cross-bridges. Conversely, we hypothesized that a warm muscle would show a reduction in the eccentric to isometric force ratio compared to normal because of a decreased ratio of weakly to strongly bound cross bridges.

Methods

Participants

This study was approved by the local ethics committee (REB Number: 15396). Ten healthy young male participants (25 ± 3 yrs, 182.4 ± 7.8 cm, 71.5 ± 5.5 kg) took part after giving written informed consent. The procedures conformed with the Declaration of Helsinki[11]. All participants were recreationally active and free from any known neuromuscular or musculoskeletal disorders. The participants did not undertake any regular hand exercises. The participants visited the lab once during

testing where orientation and data collection took place.

Experimental Setup

The experimental timeline is outlined in Figure 1. Thumb adduction force and carpometacarpal angular displacement were measured using a custom-designed dynamometer, as explained in detail elsewhere[12](Figure 2).

Briefly, the left hand was immobilized with a reusable clinical cast internally lined with a cooling/heating pad extending to the hand which was controlled by a Gaymar T/Pump localized temperature system (Model TP700 series, Gaymar Industries Inc., Orchard Park, NY, USA). A 0° reference angle was defined for each subject as the highest degree of thumb adduction possible before the dynamometer arm came in contact with the cast. Thumb angles increased with abduction, ranging from 0-40°. A thermometer was attached using tape directly on the skin above the location of the adductor pollicis in the left hand.

Electrical Stimulation

All experiments were performed using electrical stimulation of the adductor pollicis muscle via the ulnar nerve, thereby excluding influences from the central nervous system. Two self-adhering Ag-AgCl surface electrodes (2 x 3 cm) were placed over the ulnar nerve to electrically stimulate the adductor pollicis. A computer-triggered stimulator (model DS7AH, Digitimer, Welwyn Garden City, Hertfordshire, UK) was used to increase the electrical current until further increases failed to produce an increase in twitch force (single 100s square-wave pulses). This current was then used to assess voluntary activation (VA) using the interpolated twitch technique for maximum voluntary contractions (MVC)[13].

Protocol

Isometric properties: Peak twitch force amplitude was determined as mentioned above. Participants then performed 1-2 MVC contractions at a thumb angle of 40° to assess individual peak force and voluntary activation (VA). Participants were encouraged verbally during all MVCs and visual feedback of the torque achieved was provided. Only subjects with VA >90% proceeded to further testing. Percent voluntary activation was calculated as:

$$VA = 1 - [\frac{superimposed\ twitch\ force}{resting\ twitch\ force}]x100$$

All testing was performed using an identical electrical stimulation protocol. Current was increased (80Hz; square wave pulses with 100s pulse width) until the evoked force reached a value between 50 to 60% of the participants MVC peak force.

Primary Variables: Participants performed six lengthening contractions at different speeds and three muscle temperatures: 1- "normal" muscle temperature in which the temperature was that occurring at room temperature; 2- "cold" in which the muscle was cooled using a 15°C water bath for 20 minutes; and 3- "warm" in which the muscle temperature was increased using a 43°C water bath for 20 minutes. Muscle temperature was calculated by using a previously established equation developed[14] where muscle temperature = 1.02 (skin temperature) + 0.89; r^2= 0.98. The angular velocities for thumb abduction were 0°/s, -20°/s, -40°/s, -60°/s, -80°/s, -160°/s and -320°/s followed by a second 0°/s isometric contraction.

The experiment always began with a passive lengthening of the muscle at 10°/s until the thumb was 40° abducted. Once 40° was reached, an active isometric contraction lasting for 500ms was administered to establish a plateau in the force readings. From this point on the testing of the angular velocities was conducted, starting at 0° and ending at 40°, in a randomized order. Once all of the different velocities were completed a second isometric contraction, identical to the mentioned above, was administered. At the end of each temperature condition electrodes were removed from the participant's arm and the left hand was submerged in the cool or warm bath for 20 minutes. The order of temperatures was fixed from "normal" to "cold" to "warm". The order of temperature exposure was fixed for practical reasons, as a pilot study (n=3) showed that if the "warm" tests preceded the "cold" tests, the muscle temperature did not drop sufficiently (Table 1). Once baths were completed the stimulating electrodes were placed at the same location using skin markings, and the thermometer was taped back over the adductor pollicis. The stimulation current for

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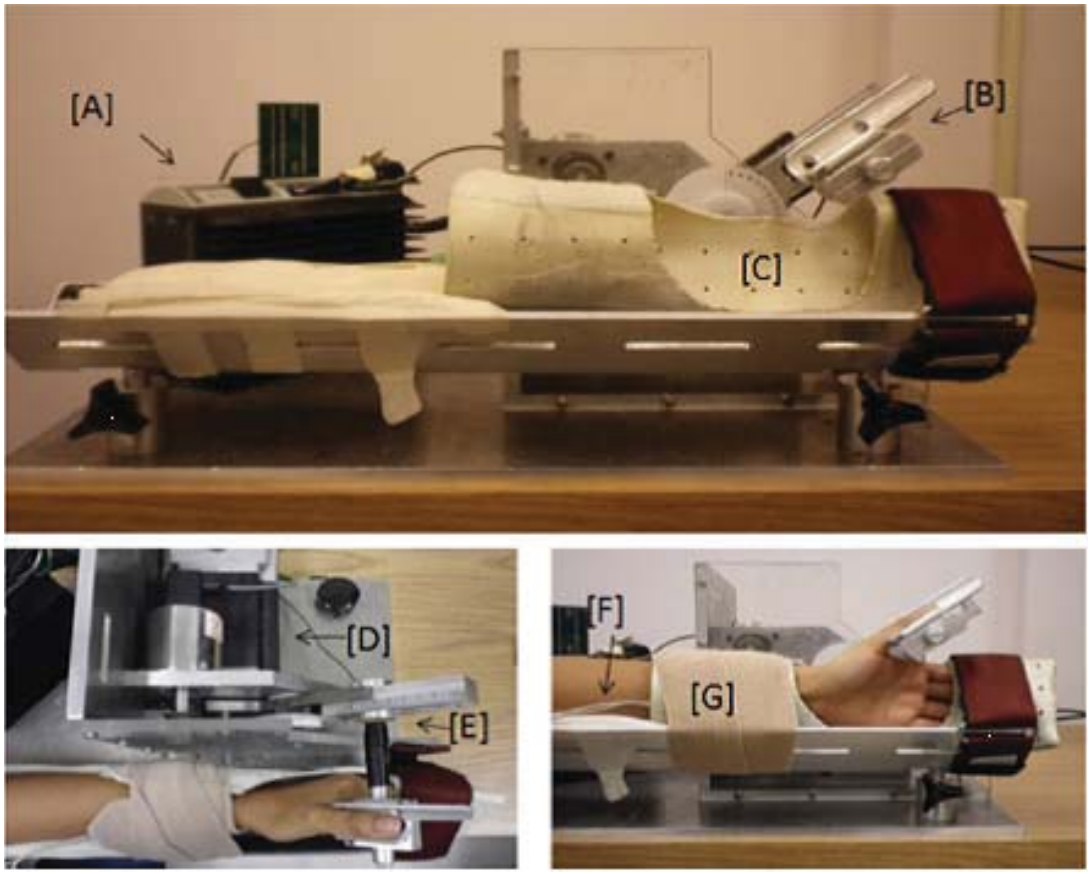

Figure 2:
The apparatus used to conduct the study included a rotary step motor (D) with a digital stepper controller. (E) represents the aluminium rod with pairs of strain gauges and the auxiliary thumb holder (B). The analog encoder is (A). The left arm (F) is fixed by the clinical cast (C) and secured with Velcro straps (G). Adapted from Fortuna, Vaz & Herzog[21].

full activation was then re-established as described above.

Data Analysis

Torque, velocity, and position data were sampled at 2000Hz and collected via an analog-to-digital converter (PowerLab System 16/35, AD Instruments, Bella Vista, Australia). All data were low pass filtered (10Hz). Instantaneous muscle stiffness (Fstiff) was determined via a change in force during a 2° quick-stretch (performed at $500°s^{-2}$) assessed 1s after the thumb position reached 40°. Twitch force was calculated as the maximal force from baseline observed in the third of three twitches applied prior to testing (Figure 1). Twitch time to peak tension[15] and twitch half relaxation time[16] was measured in the third of the three twitches at the beginning of the experimental protocol. Twitch time to peak tension was calculated from the onset of twitch force to the achievement of peak twitch force[15]. Twitch half relaxation time (HRT) was calculated as the time from peak torque occurrence until the torque had dropped to 50% of its peak value[16]. The tetanic HRT was calculated from the last electrical pulse in the 80Hz isometric contraction until force had dropped to 50% of its value at the instant of the last electrical pulse. Voluntary activation was assessed by a maximum voluntary contraction using the interpolated twitch technique (ITT)[13]. Peak eccentric force was determined as the peak force observed during the active stretch. Passive force was determined as the steady-state force following passive stretching. Active eccentric force was determined by

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Condition	Pre (Nm)	Post (Nm)
Normal	86.1 ± 25.6	95.1 ± 23.5
Cold	62.8 ± 16.6*	62.9 ± 29.6*
Warm	83.7 ± 27.6	81.1 ± 21.8

Table 1: *Peak isometric force following passive stretch pre and post conditions. Average peak force of the adductor pollicis prior to and following each temperature condition. * indicates significantly different than normal (P<0.05). Values represent mean ± SD.*

subtracting the passive eccentric force from the peak eccentric force. Peak isometric force was determined as the peak force at a thumb angle of 40°. Passive isometric force was calculated at 40°, which was subtracted from the peak isometric force taken at 40° to calculate active isometric force.

Statistical Analysis

A one way analysis of variance (ANOVA) was performed to assess changes in peak twitch force, twitch time to peak tension (TPT), peak tetanic force at 80Hz stimulation, HRT for twitch and tetanic stimulation (80Hz) and passive and active eccentric force as a function of muscle temperature. A two way ANOVA was performed to assess changes in the eccentric to isometric ratio and stiffness as a function of thumb abduction velocity and muscle temperature. When significance was observed a *post hoc* analysis using unpaired t-tests was performed with a Bonferroni correction. The level of significance for all tests was set at P<0.05. All tables are presented as means ± standard deviations (SD).

Results

Isometric properties: All isometric properties are shown in Table 2. Muscle temperatures for the three temperature conditions were significantly different from each other, with the cold muscle condition being 10.9 ± 2.0°C lower and the warm muscle condition being 5.7 ± 2.0°C higher than the normal muscle temperature (P<0.05). Cold muscles had a 33.8% lower twitch force than normal temperature muscles (P<0.05), but there was no difference in twitch force between warm and normal temperature muscles (P>0.05).

The twitch time to peak tension (TPT) was 142.2% and 111.9% longer for the cold compared to the warm (P<0.05) and the normal temperature muscles, respectively (P>0.05 for both comparisons), but there was no difference between the warm and normal temperature muscles (P<0.05). Twitch HRT was 316.2% and 214.0% longer in cold compared to warm and normal temperature muscles, respectively (P<0.05 for both comparisons), but was not significantly different between warm and normal temperature muscles (P>0.05).

The isometric tetanic force for the normal temperature condition was 90.1% higher and 18.0% lower compared to the cold and warm temperature muscles, respectively (P<0.05, P<0.05). The HRT for the tetanic contraction was 206.7% longer (P<0.05) for the cold compared to the normal temperature muscles (P<0.05), while there was no difference between the normal and warm temperature conditions (P>0.05).

Order of testing:: The isometric forces measured at the beginning and end of each temperature condition, and at the beginning and end of the entire experiment, were similar (P>0.05) (Table 1).

Lengthening contractions: Thumb abduction velocity and muscle temperature had significant effects on the eccentric to isometric force ratio. However, there was no significant interaction between these two main effects (P=0.95). Post hoc testing showed that in comparison to the 20°/s condition, the 320°, 160° and 80°/s eccentric to isometric force ratios were significantly increased (P<0.05, respectively Figure 3). The eccentric to isometric force ratio was 41.1% and 54.0% greater for the cold compared to the warm and normal muscle temperature conditions (P<0.05), while there was no difference between warm and normal muscle temperature conditions (P>0.05) (Figure 3).

Instantaneous stiffness: Thumb abduction velocity and muscle temperature had significant effects on muscle stiffness (P<0.05), but there were no interaction effects (P>0.05). The stiffness values were higher for the faster velocities (i.e., 60°, 160°, and 320°/s) as compared with the 20°/s condition

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Characteristic	Normal Temperature	Cold Temperature	Warm Temperature
Muscle Temperature (C°)	29.1 ± 2.0	18.2 ± 2.0*	34.8 ± 1.9*
Twitch Torque (Nm)	6.5 ± 1.3	4.3 ± 1.6*	7.5 ± 1.4
Twitch TPT (ms)	90.2 ± 9.0	191.1 ± 36.8*	78.9 ± 3.8
Twitch HRT (ms)	70.3 ± 16.1	220.6 ± 35.1*	53.0 ± 5.1
MVC Force (Nm)	109.5 ± 22.7	-	-
80Hz Torque (Nm)	53.8 ± 9.9	28.3 ± 4.1*	45.6 ± 5.6*
80Hz HRT (ms)	109.5 ± 18.0	245.7 ± 51.7*	80.1 ± 5.4
80Hz Torque (% MVC)	50 ± 10	26 ± 4*	43 ± 6

Table 2: *Forces and times for base line muscle properties conducted in all conditions. Time to peak tension (TPT), half reaction time (HRT), maximal voluntary contraction (MVC). Values are means ± SD. * indicates significance in comparison to normal (P>0.05).*

(P<0.05) (Figure 4). Across temperatures, isometric stiffness in the cold temperature condition was 37.9% greater than that measured for the normal temperature condition (P<0.05). There was no difference in stiffness between the warm and normal, as well as the warm and cold temperature conditions (P>0.05) (Figure 5).

Discussion

Muscle Temperature: Temperature and angular velocity effects on the eccentric to isometric force ratios were investigated in young males. Our heating and cooling protocols successfully influenced muscle temperatures and affected muscle contractile properties. Muscles had an increased eccentric to isometric force ratio in the cold compared to the normal condition, but there was no difference between warm and normal. The increased eccentric to isometric force ratio in cold compared to normal was in support of our initial hypothesis. However, our hypothesis was not fully supported for comparisons of force ratios between warm and normal conditions. This latter result may be due in part to the small change in muscle temperature from the normal (29.1 ± 2.0°C) to the warm conditions (34.8 ± 1.9°C), and the reported lack of force dependence on temperature above 25°C in mammalian muscle[7].

Isometric twitch and tetanic forces have been shown previously to increase with increasing temperatures, while instantaneous muscle stiffness has been reported to remain roughly the same across temperatures [3,17,18]. From these observations it can be assumed that there is an increase in the average force per cross-bridge as temperature increases, potentially caused by a shift to a greater proportion of strongly compared to weakly bound cross-bridges with increasing temperatures[3]. In the present study, we found that isometric force (0°/sec) increased with increasing temperature. However once muscle temperature exceeded room temperature, there was no further change in isometric force. Instantaneous stiffness for the isometric contractions was greater in the cold than normal temperature, but was not different between the warm and normal temperature conditions. Changes in stiffness across temperatures were different from those reported by Lee & Herzog[4] who did not observe a change in force across muscle temperatures, but found an increase in stiffness with decreasing temperatures, suggesting that the force per cross-bridge increased with increasing temperatures. The experiments by Lee & Herzog[4] were conducted with frog muscles, which have been shown to adapt to cool conditions to maintain peak force[19], and therefore may demonstrate the same temperature-dependence of muscle properties as mammalian muscles.

Angular lengthening velocities: The eccentric part of the force-velocity relationship[9] is associated with an increase in force with increasing lengthening velocities, up to a certain threshold velocity. At this threshold the muscle does not produce any more force with increasing lengthening velocity[9]. This translates to an increased eccentric to isometric force ratio for increasing stretch velocities up to the threshold mentioned, which has been observed in young and old populations[10,20]. As expected, we found a general increase in eccentric to isometric force ratio at angular velocities $\geq 80°/s$ compared to the slowest eccentric velocity (20°/s). There was no significant change

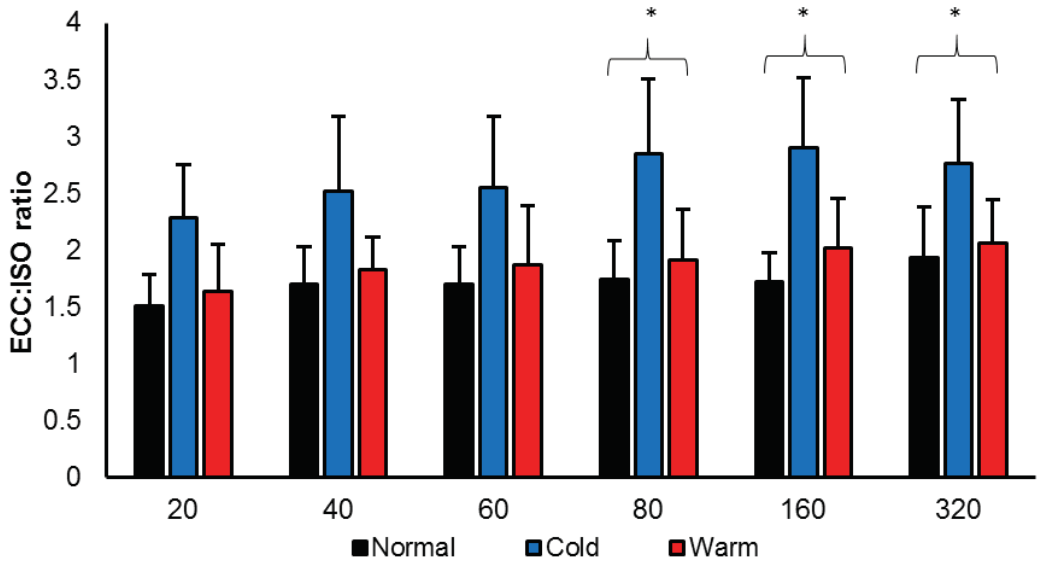

Figure 3:
Average eccentric to isometric force ratios in all three temperature conditions (normal, cold, warm) across six velocities (20°, 40°, 60°, 80°, 160°, 320°sec). Cold was greater than normal and warm across all velocities. * denotes velocity-dependent significance between ratios in comparison to 20°/sec ($P<0.05$). Values are mean ± SD.

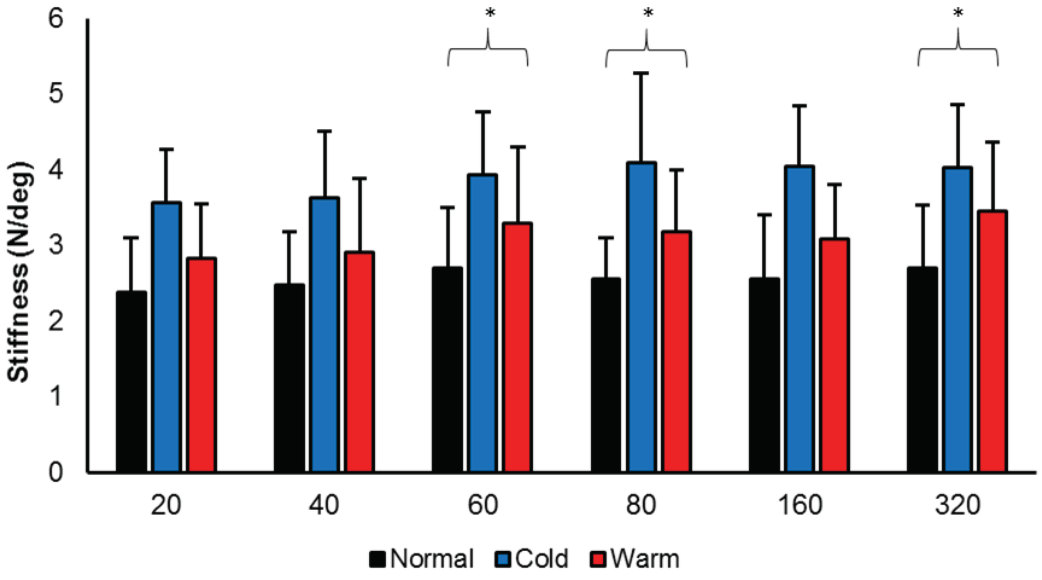

Figure 4:
Average instantaneous muscle stiffness across muscle temperatures (normal, cold, warm) and velocities (20°, 40°, 60°, 80°, 160°, 320°sec). Within each temperature, stiffness was only greater for the cold as compared with normal condition. * denotes significance between grouped velocities stiffness in comparison to 20°/sec ($P<0.05$). Values are mean ± SD.

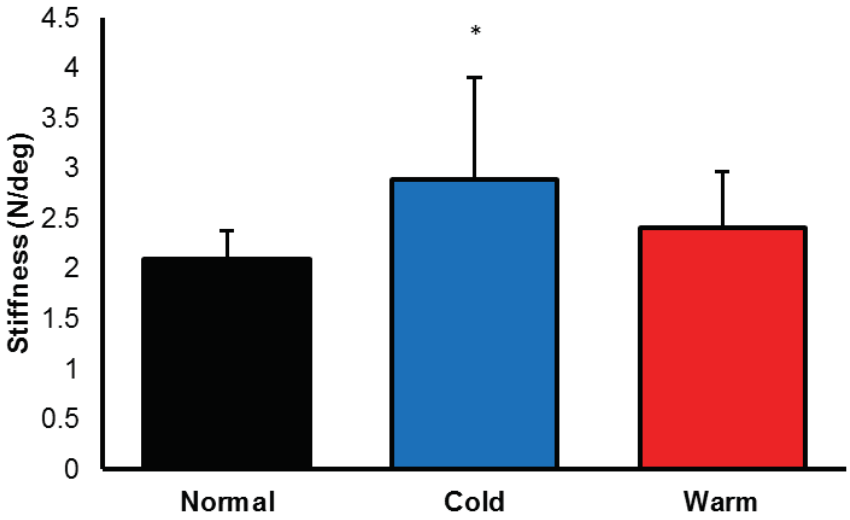

Figure 5:
Average instantaneous stiffness of isometric force following a passive stretch at the beginning of each temperature condition. * denotes significant difference from Normal ($P<0.05$). Values are mean ± SD.

in the eccentric to isometric force ratio at angular velocities higher than 80°/sec. This observation is consistent with earlier results on the eccentric to isometric force ratio for eccentric contractions [10].

Proposed mechanisms of the temperature and velocity dependence of force: The temperature dependence of eccentric force within the eccentric to isometric force ratio may be explained in part by the altered contractile kinetics in cold compared to warm muscles. In cold conditions compared to warm conditions there tends to be an increase in the eccentric to isometric force and stiffness ratio, possibly because there is an increasing proportion of weakly to strongly bound cross-bridges with decreasing muscle temperature. Since force increased from the cold to the normal temperature conditions with a simultaneous decrease in stiffness, it seems that the force per cross-bridge increased with increasing muscle temperature, as reported in the literature[3,4].

The eccentric to isometric force ratio and the absolute stiffness were not different between the warm and normal temperature conditions. The constant stiffness for the warm and normal muscle temperature conditions suggests that the proportion of attached cross-bridges remains similar for these two temperatures. Since the isometric force between the normal and warm temperature conditions remained the same (Table 1), it seems that the force per cross-bridge is the same for these two temperatures. This result goes against convention, as it is typically accepted that as temperature rises the force per cross-bridge increases as well[4]. However, due to the sigmoidal relationship of the isometric force and temperature[6],we suspect that there is a temperature dependent theoretical maximum to the equilibrium proportion of strongly to weakly bound cross-bridges which was reached in the present experiments.

Velocity dependence of eccentric force can be explained in part by the slowing of cross-bridge cycling during the active stretch, perhaps owing to a similar rate of detachment and longer time attached[8]. Ultimately, this means the cross-bridges remain attached to the actin filament for a longer period of time. Because the myosin head remains attached for a longer period of time during stretch, the cross-bridge strain associated with the active stretch is greater, thus producing a greater force than during the purely isometric contractions. Further, when the velocity of the stretch is increased the cross-bridge strain increases, on average, as cross-bridges get dragged to greater distances away from their equilibrium conditions[5]. Our results support this increasing force with increased velocity, with a significant difference at 80, 160 and 320°/sec compared to the 20°/sec.

Order of testing: The warm temperature condition experiments were always performed last. This

order of testing could have resulted in residual fatigue or muscle damage for the warm condition experiments, which in turn, may account for the significant decrease in the tetanic force in the warm compared to the normal temperature condition experiments. This loss in peak force for the warm temperature experiments may cause an artificially elevated eccentric to isometric ratio. Assuming this is the case and that the eccentric force was not effected by fatigue or damage, we would have seen a decrease in the eccentric to isometric ratio in the warm condition, and with the accompanied stiffness tests we would have seen the potential for an increase in the force per cross-bridge as mentioned in the literature[4]. However this is unlikely, as we show no reduction in the isometric tests conducted at the beginning and end of each temperature condition (Table 1). Further, there is no difference between the first isometric forces recorded during the testing (first isometric in normal condition) to the last (second isometric in warm condition).

Conclusion

We found that in young men the eccentric to isometric force ratio is increased when the muscle is cooled, and showed no difference when muscle temperature was increased in comparison to the normal temperature condition. The velocity of stretching had an effect on the eccentric to isometric force ratio at velocities of 80°/sec and greater. Based on these findings, we propose that as muscle temperature rises, the force per cross-bridges increases until normal physiological temperature is reached; then, further increases in temperature do not increase force per cross-bridge. Finally, our data indicate that at the warm and normal muscle temperatures, the proportion of strongly bound cross-bridges may reach a limit, thereby preventing a reduction in eccentric to isometric force ratio in warm muscle.

Acknowledgements

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Conflict of Interest Disclosure:

The authors have no conflicts of interest to disclose.

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In situ titin properties at long lengths when Ig domain folding/unfolding is prevented

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Titin, also known as connectin, is the largest known protein and was discovered in the mid-1970s and consists of Immunoglobulin (Ig) domains that flank N2A and PEVK segments. At long lengths and high force these Ig domains unfold. There is growing evidence that titin may change its stiffness by attaching its proximal portion to actin upon activation. If so folding/unfolding of Ig domains may become physiologically relevant. This is of interest because Ig domain folding/unfolding is associated with a great loss of energy, but preventing such folding/unfolding has been shown to result in a virtually elastic behaviour with no energy loss in isolated titin molecules. Therefore, the purpose of this study was to test titin properties in situ within sarcomeres at lengths where Ig domain unfolding has occurred while preventing folding/unfolding of Ig domains during small stretch shortening cycles. **Keywords:** muscle; titin; sarcomere.

Introduction

Titin, also known as connectin, is the largest known protein and was discovered in the mid-1970s[1,2]. In striated muscles, titin spans the half sarcomere, from Z-band to M-line (Figure 1). It acts as a molecular spring in the region between its Z-band and thick filament attachments, the I-band region[3], thereby stabilizing the myosin filaments in the centre of sarcomeres[4], providing passive force to muscle[5], and allowing for force transmission between sarcomeres.

The spring-like elements of titin in the I-band region of skeletal muscle consist of two Immunoglobulin (Ig) domains that flank the N2A and PEVK segments (Figure 1). Upon muscle stretching, the randomly oriented Ig domains are aligned first, followed by stretching of the PEVK segment, and finally the unfolding of Ig domains which has been thought to only occur at para-physiological muscle lengths[6,7].

Aside from its acknowledged role in passive force production, titin has recently been implicated in regulating active forces by changing its stiffness, and therefore its force when muscles are actively stretched[8–13]. It is known that such changes in titin stiffness occur when, upon activation and calcium influx into the sarcoplasm, calcium ions bind to specific sites on titin, thereby changing the unfolding characteristics of titin, or specifically, the PEVK[8,9], and Ig domains[14]. Furthermore, there is accumulating evidence that titin may change its stiffness by attaching its proximal portion (proximal Ig domain, N2A region, and possibly some of its PEVK domain) to actin upon activation, thereby leaving the distal Ig domain as the only remaining spring element in activated muscle[12,13,15]. If so, the folding/unfolding properties of the Ig domain would become physiologically relevant, as such folding/unfolding would occur during active (but not passive) muscle stretching within the physiological range of muscle excursions. This is of

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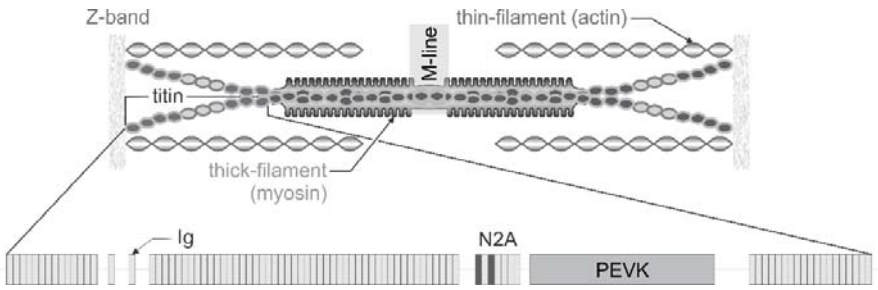

Figure 1:
Schematics of a sarcomere with the contractile filaments, actin and myosin, and the structural protein titin. Titin acts as a spring in the region between its attachments into the Z-band and the myosin filament, a region that is composed of two tandem immunoglobulin (Ig) domains, the N2A, and the PEVK segment. Each of these individual segments has spring like properties of different stiffness, thereby producing a complex mechanical structure of serially arranged springs that come into play at distinct sarcomere lengths (and thus, distinct passive forces).

particular interest since Ig domain folding/unfolding is associated with a great loss of energy[6,7,16], but preventing such folding/unfolding has been shown to result in a virtually elastic behaviour with no energy loss in isolated titin molecules. However, titin properties have been shown to differ substantially between isolated titin preparations and titin in its physiological in situ environment within a sarcomere[7].

Methods

Preparation: Myofibrils were prepared for mechanical testing as described previously[17,18]. Briefly, small pieces of muscle were harvested from rabbit psoas, and were isolated to obtain short myofibrils. Isolated myofibrils were then immersed into a bath on top of an inverted microscope in a rigor solution (see solutions below). After ten minutes, the rigor solution was replaced with a low calcium relaxation solution (see solutions below) that prevented active force production. Myofibrils in suspension were then washed away, leaving those attached to the bottom cover glass. Myofibrils of appropriate length (typically 6-12 sarcomeres in series) with a distinct striation pattern were selected for mechanical testing by attaching them at one end to a silicon nitride lever for force measurements (stiffness of 68pN/nm, force resolution of 0.5nN) and at the other end to a rigid glass needle attached to a motor for controlled, sub-nanometre step size, length changes (Figure 2).

The image of the attached myofibril was projected onto a high density photo diode array (Schafter/Kirschoff, Hamburg, Germany, resolution of 7nm) for identification of the A- and I-bands, Z-bands, and the calculation of sarcomere lengths from Z-band to Z-band or between the centroids of adjacent A-bands if Z-bands were not clearly visible.

Solutions: The rigor solution (pH 7.4) was composed of (in mM): 50 Tris, 100 NaC1, 2 KC1, 2 MgC12, and 10 EGTA. Protease inhibitors were added to the final solution, in the following concentrations (in pM): 10 leupeptin, 5 pepstatin A, 0.2 PMSF, 0.5 N, and 0.5 DlT. The relaxing solution (pH = 7.0; pCa2+ = 8) was composed of (in mM): 10 MOPS, 64.4 K+ proprionate, 5.23 Mg proprionate, 9.45 Na2S04, 10 EGTA, 7 ATP, 10 creatine phosphate.

Protocol: Myofibrils (n=9) were stretched passively from an average sarcomere lengths of about 3.0m to an average sarcomere length of about 5.5m at a speed of 0.1sarcomere lengths/s, and then held at that length for 120s for stress relaxation to occur and passive force to reach a near steady-state (Figure 3). Immediately following the 120s, hold, myofibrils were subjected to ten shortening-stretch cycles of approximately 0.5m/sarcomere magnitude and then released to the original lengths of about 3.0m/sarcomere.

Analysis: The mean force relaxation (1SD) for the two minute stress relaxation period was evaluated as the percentage decrease of force from the peak force at the end of stretch, to the (nearly) steady-state force averaged across the last five seconds of the 2 minute holding period (Figure 3). The mean decrease in force (1SD) for the ten stretch-shortening cycles following the stress relaxation period was calculated

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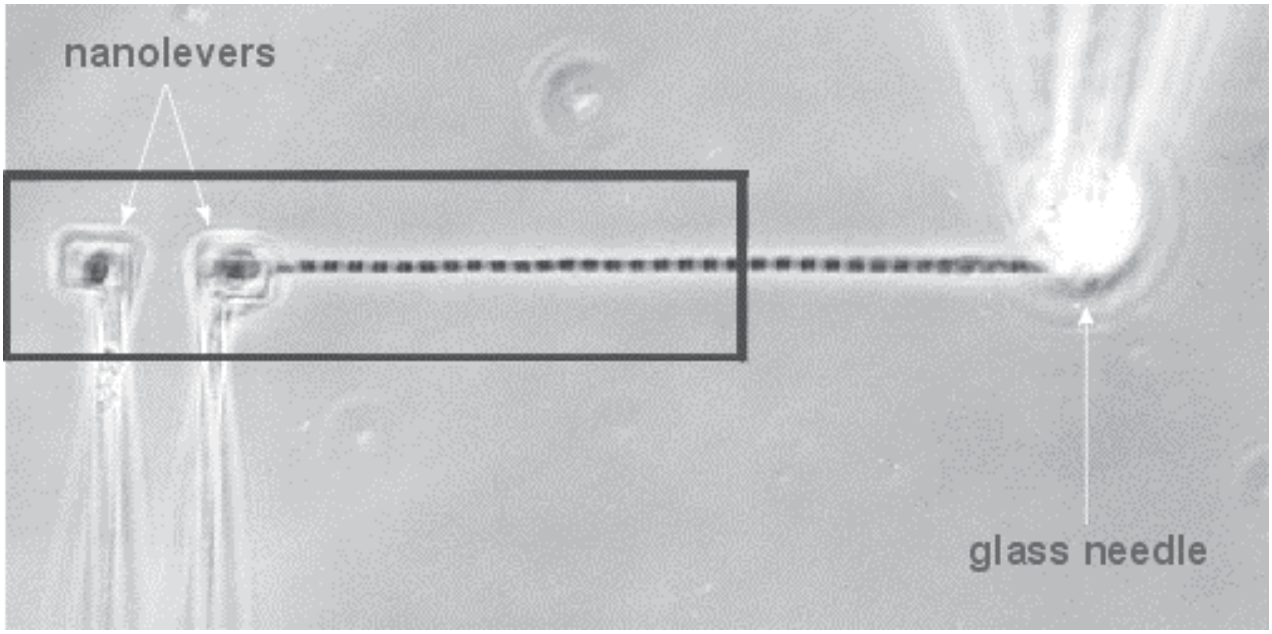

Figure 2:
Experimental setup showing a myofibril comprised of about 30 serially arranged sarcomeres. The myofibril is attached at the left end to one nano-lever of a pair for force measurements and at the right end to a glass needle that is connected to a motor that can impose computer controlled length changes with a resolution of less than 1nm.

as the percentage decrease of the peak force from the first to the tenth stretch-shortening cycle expressed as the average decrease per cycle (Figure 3). Finally, the mean hysteresis (1SD) (energy loss) for each of the ten stretch-shortening cycles following the relaxation period was calculated as the percentage energy loss relative to the energy during the stretch across all ten cycles and all nine myofibrils.

Results

Holding the myofibrils for two minutes at the final stretched length of about 5.5m/sarcomere resulted in a force relaxation averaging 35"%" (6"%"), and resulted in near steady-state forces by the end of the hold, indicating that Ig domain unfolding had been essentially complete. The following ten stretch-shortening cycles resulted in an average decrease in force of 0.7"%" (0.9"%") per cycle, thereby indicating an essentially elastic behavior in terms of force retention. There was a consistent average loss of energy (hysteresis) for the ten stretch-shortening cycles across all myofibrils of 13"%" (3"%") (Figure 4).

Discussion

The purpose of this study was to test titins properties in situ within sarcomeres at lengths where Ig domain unfolding has occurred, while simultaneously preventing folding/unfolding of Ig domains for small stretch-shortening cycles. We hypothesized that titin properties would be virtually elastic for such conditions, as has been found in isolated titin preparations tested using laser trapping techniques[6]. In order to prevent folding of Ig domains, testing was performed at very long sarcomere lengths (¿4.5m) thereby ensuring that refolding of Ig domains was highly unlikely[6,7]. In order to prevent unfolding of Ig domains during the ten stretch-shortening cycles, we let myofibrils stress-relax at long lengths (approximately 5.5m/sarcomere) for two minutes, resulting in a force loss averaging 35"%" and reaching near-steady-state conditions ensuring that Ig domain unfolding for the subsequent stretch-shortening cycles was minimal. Since force decrease during the stretch-shortening cycles following stress relaxation averaged less than a percent per cycle, we feel confident that Ig domain unfolding played no (or only a minor) role in our results. In previous

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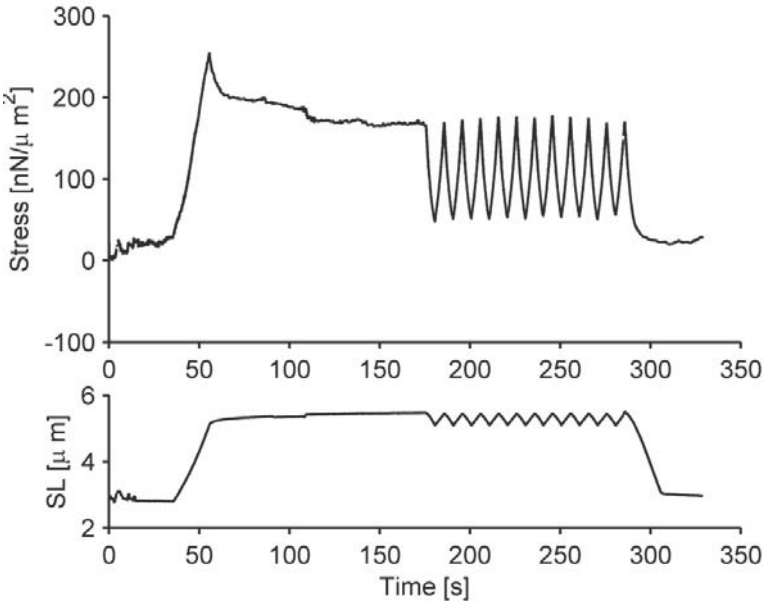

Figure 3:

Stress (force per cross-sectional area) vs. time and sarcomere length (SL) vs. time trace for a representative myofibril that was stretched form an average sarcomere length of about 3.0m to an average sarcomere length of about 5.5m, held for two minutes at the final length, and then subjected to ten stretch-shortening cycles of about 0.5m/sarcomere. Note that the maximum and minimum forces during the ten stretch-shortening cycles remained virtually the same, indicating an essentially elastic behaviour of the myofibril for these conditions.

work, we performed similar experiments using ten stretch-shortening cycles at long sarcomere lengths, but in those experiments no stress relaxation preceded the stretch-shortening cycles (Figure 4B)[7]. This resulted in a relatively great decrease in peak forces in the cycling period. We interpreted these results as being affected by Ig domain unfolding, which resulted in substantial force loss throughout the stretch-shortening cycles and hystereses decreasing from the first (42"%") to the last cycle (7"%") averaging 18"%" (12"%")[7]. Here, we ensured that Ig domain folding/unfolding was minimized, possibly completely prevented, and, as a consequence, peak forces during the stretch-shortening cycles remained virtually constant for many tests (e.g. Figure 4A). However, this did not result in the anticipated elastic behavior of titin within the myofibrils as had been observed for isolated single titin preparations, but resulted in a consistent hysteresis averaging 13"%" that remained essentially constant across the ten stretch-shortening cycles[6,19]. Of course, there is always the possibility that the isolated titin results by Kellermayer et al. (1997) are not correct. However that seems rather unlikely as their experiments were performed extremely carefully and were confirmed later in independent experiments[19]. It could also be that our results, with a consistent hysteresis, were not correct. However, this is also rather unlikely since the observed hystereses were consistent in magnitude and were observed in all ten trials of all myofibrils. However, if isolated titin properties, as observed by others[6] do not match titin properties observed here in situ, then titin might behave differently in the intact sarcomere compared to how it behaves when tested as an isolated protein. The result that titin peak force during the ten stretch-shortening cycles remained essentially constant suggests that titin behaves elastically within the sarcomere, and that the hysteresis is not caused by the stretching and shortening of the titin molecule, but is associated with titins in situ behavior. Tentatively, we suggest that in the in situ condition, titin binds to another protein upon shortening of the sarcomere and associated force loss, while this bond is broken during stretching giving the stretch phase additional energy compared to the shortening phase. The

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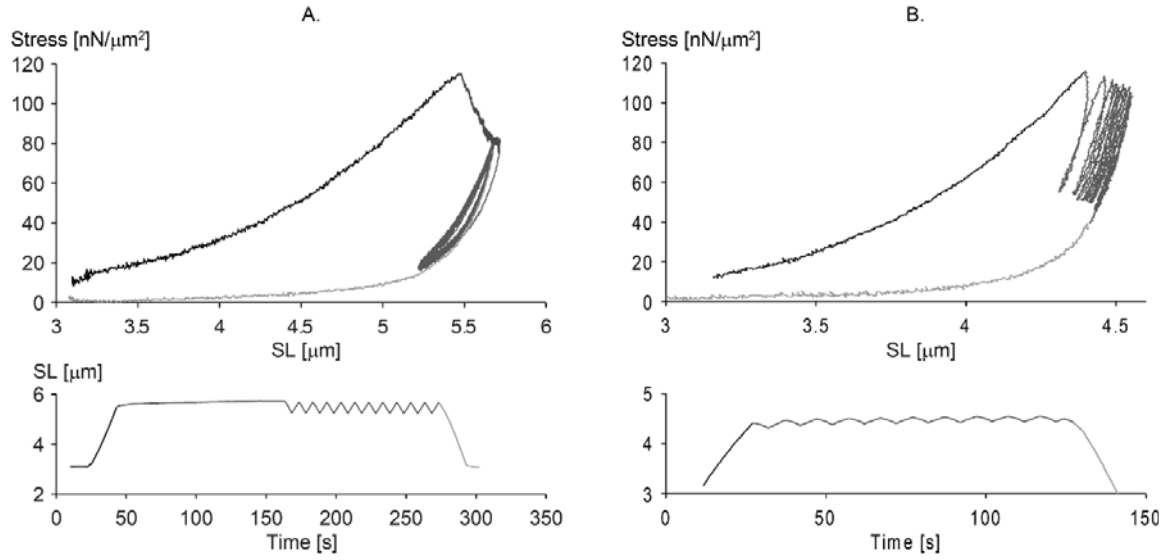

Figure 4:

Stress (force per cross-sectional area) vs. time and sarcomere length (SL) vs. time trace for a representative myofibril that was stretched form an average sarcomere length of about 3.0m to an average sarcomere length of about 5.5m, held for two minutes at the final length, and then subjected to ten stretch-shortening cycles of about 0.5m/sarcomere. Note that the maximum and minimum forces during the ten stretch-shortening cycles remained virtually the same, indicating an essentially elastic behaviour of the myofibril for these conditions.

most likely candidate for such loose binding of titin is actin. Therefore we suggest that in the absence of Ig domain folding/unfolding titin behaves elastically in isolation, but binds/unbinds to another protein (actin) upon shortening/stretching, thereby producing the observed hysteresis of consistent 13"%" magnitude with little variation across cycles and myofibrils (3"%" standard deviation). All experiments were performed passively (i.e. at low calcium concentrations) and at long sarcomere lengths where a great number of Ig domains would have been unfolded[6,7]. Although the sarcomere lengths used here were beyond the physiological limits of the rabbit psoas muscle in vivo[7], Ig domain unfolding as studied here is likely relevant for active muscle contractions, as the proximal part of titin is thought to bind to actin upon muscle activation[13,15], thereby just leaving the distal Ig domain as the single spring element in activated muscles. Thus, studying passive sarcomeres at long lengths might provide insight into titins properties in active muscles within the physiologically relevant working range.

Conclusion

In the absence of Ig domain folding/unfolding, titin properties measured within the structural environment of a sarcomere are different from those of single isolated titin preparations. While Ig domain unfolding likely plays no role at physiological sarcomere lengths in passive muscle, Ig domain unfolding is likely a normal physiological occurrence in active muscle stretching.

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Cognitive Insight in Youth at Clinical High Risk of Psychosis

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Cognitive insight reflects ones Self-Reflectiveness (recognition of dysfunctional reasoning, corrigibility) and Self-Certainty (overconfidence). In schizophrenia, lower Self-Reflectiveness and higher Self-Certainty has been associated with severity of symptoms and poor functioning. There is some evidence that lower Self-Reflectiveness and higher Self-Certainty are associated with attenuated symptoms in youth at clinical high risk (CHR) of psychosis. The present study evaluated in a CHR sample the relationship between cognitive insight, attenuated symptoms, and current functioning, and evaluated change in cognitive insight at baseline and 1-month follow-up. Twenty-four individuals at CHR of psychosis completed the Beck Cognitive Insight Scale. Attenuated psychotic symptoms were assessed with the Scale of Prodromal Symptoms and functioning with the Global Functioning Social and Role scales. Self-Reflectiveness, Self-Certainty, and Composite Index scores were correlated with clinical and functional variables. In addition, cognitive insight levels were compared at baseline and 1-month follow-up. Trends were observed toward both increased attenuated perceptual abnormalities/hallucinations and higher Self-Reflectiveness, and increased avolition and increased Self-Reflectiveness. Cognitive insight did not significantly correlate with social or role functioning. Cognitive insight scores did not significantly differ between baseline and 1-month follow-up. These findings provide little evidence for a relation between cognitive insight and clinical and functional variables in CHR, and suggest that cognitive insight remains stable over a 1-month time period in our sample. These data add to a growing body of literature on cognitive insight across the schizophrenia spectrum. Keywords and Definitions: Clinical high risk of psychosis: An individual who experiences attenuated or brief intermittent psychotic symptoms, or has a genetic risk for psychosis and functional decline. Cognitive insight: Self-Reflectiveness, ones recognition of dysfunctional reasoning and openness to external feedback, and Self-Certainty, overconfidence in beliefs and judgments. Clinical variables: Attenuated positive symptoms and negative symptoms. Current functioning: Social functioning, an individuals ability to interact with others beyond their family, and role functioning, an individuals ability to be self-sufficient.

Introduction

Psychosis is a severe mental illness in which the person loses contact with reality. It is characterized primarily by delusions, or fixed false beliefs, and

hallucinations, which are false sensatory experiences. Insight is one important clinical considering in patients with psychosis. Lack of clinical insight (ie, poor awareness of illness) is another core feature of schizophrenia[1] which is one type of psychosis. The clinical concept of insight focuses on the patients understanding that their symptoms and behavior are a consequence of their mental disorder, the need and efficacy of their treatments, and the social consequences of the disorder (i.e. stigma)[2,3].This form of insight is determined by evaluating an individuals behavior through a clinical interview and is valuable for ascertaining the proper diagnosis, prognosis, and treatment in people with schizophrenia.

Essential to the understanding of clinical insight is an understanding of the individuals ability to distance themselves from their distorted beliefs and misinterpretations, contemplate their rationality, and recognize inaccurate conclusions. Beck and colleagues[4] developed the Beck Cognitive Insight Scale (BCIS) to psychometrically assess these cognitions in people with psychotic disorders. Two constructs are measured: Self-Reflectiveness, defined as ones willingness to acknowledge fallibility, consider alternate explanations, and openness to external feedback, and Self-Certainty, which addresses overconfidence. In order to account for a potential dampening of Self-Reflectiveness caused by an individuals level of certainty about their beliefs, a Composite Index can also be calculated through subtracting ones Self-Certainty score from their Self-Reflectiveness score[4]. A series of studies have reported that relative to healthy people, individuals with psychotic disorders typically endorse lower Self-Reflectiveness and higher Self-Certainty, and this is interpreted as poorer cognitive insight[5]. Developing a better understanding of clinical insight depends upon exploring a patients ability to identify their distorted beliefs and misinterpretations, reflect on these concepts rationally, and recognize flawed conclusions. Poor cognitive insight is indeed one of many cognitive distortions observed in people with schizophrenia[6]. For example, people with schizophrenia tend to make hasty decisions with little evidence *(jumping to conclusions bias)*[7], show increased confidence in incorrect responses *(knowledge corruption)*[8], and an unwillingness to downwardly adjust plausibility ratings to reflect recently encountered disconfirmatory evidence *(Bias Against Disconfirmatory Evidence)*[9].

Several studies have evaluated the relationship between cognitive insight and positive symptom severity in people with psychosis. One study found in a sample of schizophrenia patients significant correlations between higher positive symptom severity and lower Self-Reflectiveness, and higher Self-Certainty, and lower Composite Index scores[10]. Another reported significant positive correlations between positive symptoms and Self-Certainty in a more chronic population of schizophrenia and schizoaffective outpatients[11]. Other studies have focused on the role of specific positive symptoms such as delusions, which are fixed false beliefs and hallucinations (sensatory experiences) for cognitive insight in this population. For example, Warman and colleagues[12]. found that people with psychosis with active delusions endorsed higher Self-Certainty and lower Self-Reflectiveness compared to patients without delusions and healthy controls. A different study reported low Self-Reflectiveness and high Self-Certainty in schizophrenia patients with delusions compared to patients without delusions, regardless of the presence or absence of hallucinations[13]. Buchy and colleagues[14] reported that first-episode psychosis patients with active delusions endorsed lower Self-Reflectiveness than patients without active delusions, but that these two groups were indistinguishable on their Self-Certainty. There is also some data suggesting that delusion proneness in non-clinical samples is associated with poor cognitive insight[15,16]. Warman et al.[15] compared a control group of undergraduate students to individuals with psychotic disorders, and reported increased Self-Certainty and lower Composite Index scores in the latter group. Furthermore, patients with delusions had higher Self-Certainty in comparison to those without delusions and controls. In contrast, patients without delusions endorsed lower Self-Reflectiveness than patients with delusions and controls. A second study attempted to replicate these results in an independent non-clinical sample of undergraduate students. Contrary to the findings of Warman et al.[15], the study found that higher delusion proneness in the non-clinical sample correlated with both higher Self-Certainty and Self-Reflectiveness[16]. In summary, the research to date suggests that hallucinations, delusions, delusional proneness may

interact with cognitive insight in people with psychosis and in non-clinical subjects high in delusion proneness.

Other studies have explored the relationship between cognitive insight and negative and depressive symptoms in people with psychotic disorders. Two studies found that higher negative symptom severity significantly correlated with lower Self-Reflectiveness, one in a multi-episode schizophrenia sample[10] and a second in a first-episode psychosis cohort[17], and a third reported that higher negative symptom severity was associated with higher Self-Certainty in a middle-aged and elderly schizophrenia or schizoaffective population[11]. No published studies have evaluated the relationship between specific negative symptoms and cognitive insight in a psychosis sample. Warman et al.[12] reported that greater depressive symptom severity was associated with higher Self-Reflectiveness in a sample of people with psychotic disorders. Another investigation reported that individuals with a psychotic or bipolar disorder had poorer cognitive insight than those with a major depressive disorder[18]. However, the majority of studies have failed to observe a relationship between depressive symptoms and cognitive insight in psychosis[4,11,17,19,20]. Taken together, there is some evidence for a relationship between negative symptoms and cognitive insight in people with psychosis, whereas the role of depression is mixed, creating an unclear picture of how cognitive insight may interact with clinical symptoms prior to the onset of psychosis.

An interesting area of research that has received scant attention is the relationship between cognitive insight and functioning in this population. This represents an important consideration, as symptom severity is known to impact on current levels of functioning[21]. In the only study to date on this topic, people with schizophrenia were divided into groups based on their current living situation, either in a nursing home or independently, and compared on cognitive insight psychosis[20]. The authors reported that relative to patients living independently, patients living in a nursing home endorsed significantly lower Self-Reflectiveness and higher Self-Certainty scores. This finding suggests that patients living in a predetermined environment have poorer cognitive insight compared patients who are able to live independently in a self-determined environment, and links cognitive insight to current functional capacity in people with psychotic disorders. The relationship between functioning and cognitive insight in CHR has not been examined, and may provide important clinical information as poor social functioning is known to increase the risk of conversion to psychosis in CHR youth[21].

Very recent research has begun to characterize cognitive insight levels in people at clinical high risk (CHR) of developing psychosis. People at CHR of psychosis show attenuated psychotic symptoms, brief intermittent psychotic symptoms, or have a genetic risk for the disorder and present with a current decline in functioning. Approximately 35% of people who are at CHR for psychosis eventually develop or convert to a psychotic disorder such as schizophrenia[22]. A first study evaluated cognitive insight in people at CHR of psychosis, patients with schizophrenia, and healthy controls[23]. The study found that CHR endorsed lower Self-Certainty and lower Self-Reflectiveness scores than the schizophrenia group, but higher Self-Certainty and similar Self-Reflectiveness scores in comparison to the healthy controls. Further analyses in the CHR group revealed no significant correlations between attenuated or sub-threshold delusional ideation or suspiciousness and scores on any cognitive insight variable. However, CHR participants who were close to meeting threshold criteria for psychotic level of persecutory ideation endorsed significantly higher Self-Certainty scores than those who did not meet this criterion. A second study compared CHR individuals to healthy controls on cognitive insight using a Japanese version of the Beck Cognitive Insight Scale[24]. Results revealed that CHR individuals endorsed significantly higher Self-Certainty compared to the control group, but that groups endorsed comparable levels of Self-Reflectiveness. In addition, a positive correlation was seen between higher Self-Certainty scores and greater sub-threshold delusional symptom severity in the CHR group, and CHR participants with attenuated delusional symptoms had significantly higher Self-Certainty in comparison to those who did not meet the designated criteria[24]. Taken together, the limited data on cognitive insight in CHR youth is somewhat consistent with finding in people psychosis, suggesting poorer cognitive insight than controls and a relation between greater attenuated delusional symptom severity and higher Self-Certainty. However,

with only two published studies on this topic, replication of findings is warranted, and further examination between cognitive insight and social functioning deserves attention given its association in schizophrenia.

There are several limitations in the literature on cognitive insight in CHR youth. Although the two studies discussed above[23,24] have provided important information on cognitive insight in CHR compared with controls, analyses of symptom data were restricted to delusional symptoms, and did not explore other symptoms that have been linked to poorer cognitive insight in psychotic samples such as negative and depressive dimensions[19]. An understanding of cognitive insight and its relation to other subclinical symptomatology in CHR could provide particularly important information on how cognitive insight interacts with symptom severity prior to the onset of psychosis. Further, the relationship between current functioning and cognitive insight in CHR youth has not been explored, and may be of clinical value as there is some evidence that poorer functioning is associated with poorer cognitive insight in people with schizophrenia[20].This may also be of clinical interest, as impaired functioning is known to predict clinical outcome in CHR individuals[21]. Finally, the longitudinal trajectory of cognitive insight has not been evaluated, and may be of clinical significance in CHR youth, as there is limited data in people with schizophrenia suggesting an improvement in Self-Reflectiveness but not Self-Certainty following inpatient treatment for a psychotic episode.

Therefore, the aim of the present study was to evaluate in a CHR sample the relationship between cognitive insight and a) total attenuated positive and negative symptoms; b) individual attenuated positive (i.e., delusions, perceptual abnormalities/hallucinations) and negative symptoms (i.e., avolition, flat affect); c) current social and role functioning; and d) change in cognitive insight over a 1-month time period. We hypothesized that increased attenuated delusions and hallucinations, greater negative symptom severity and lower in current functioning would correlate with higher Self-Certainty and lower Self-Reflectiveness. The analysis of change over time was exploratory; therefore, no specific hypotheses were formed.

Methods

Participants

Twenty-four youth at CHR of psychosis were recruited at the University of Calgary, Alberta, Canada. All participants met the Criteria of Prodromal Syndromes (COPS) using the Structured Interview for Prodromal Syndromes (SIPS) [25]. Participants were excluded if they met criteria for any current or lifetime Axis I psychotic disorder, IQ<70, past or current history of a central nervous system disorder or DSM-IV criteria for current substance dependence disorder. Further description on recruitment, inclusion and exclusion criteria, and participant details can be found in Addington et al.[26].

The SIPS and Scale of Prodromal Symptoms (SOPS)[25] were used to assess the criteria for a prodromal syndrome and attenuated positive symptom severity. The COPS was used to address the manifestation of prodromal syndromes as Brief Intermittent Psychotic syndrome, Attenuated Positive Symptom Syndrome, and Genetic Risk and Deterioration Syndrome.

Beck Cognitive Insight Scale (BCIS)

Cognitive insight was assessed with the 15-question self-report BCIS[4]. Nine questions assess Self-Reflectiveness and six address Self-Certainty. Composite index scores (Self-Reflectiveness Self-Certainty) were also calculated. Each question is rated on a 4-point scale, from 0 (does not agree at all) to 3 (agrees completely). Global Functioning Scale: Social Global Functioning Scale: Role (GF:S GF:R) were used to assess participants current level of functioning[27]. The GF:S focuses on an individuals ability to be social and generate interactions with others beyond their family. The GF:R focuses on an individuals ability to be independent and support themselves with regards to their current situation. Both Global Functioning Scales are rated on a 10-point scale, with 10 equivalent to the highest level of functioning.

Procedure

Post-training agreement on determining the prodromal diagnoses was excellent (kappa=0.90). J.A. conducted a comprehensive clinical assessment to determine if entry criteria were met. A trained

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Characteristic	Mean (SD)	Range
Age (years)	16.1 (2.24)	13 to 20
Education (years)	10.0 (1.84)	7 to 13
BCIS scores		
Self-Reflectiveness	11.9 (3.43)	6 to 18
Self-Certainty	6.25 (3.10)	0 to 12
Composite Index	5.67 (5.02)	-1 to 15
	N (%)	
Gender: M:F (%)	11:13 (46:54)	

Table 1: *Demographic and cognitive insight characteristics of the CHR sample (N=24). BCIS, Beck Cognitive Insight Scale; SD, Standard deviation.*

administrator not involved in the treatment of the participant conducted a clinical interview and assessment, which included the BCIS. Prior to the clinical interview, participants were described the details of the study and provided written informed consent. Participants who were under 16 years of age acquired parental consent from their parents/ legal guardians. The University of Calgary Conjoint Health Research Ethics Board approved the study.

Statistical Analysis

BCIS scores were normally distributed; therefore, Pearson correlations were used to examine the relationship between Self-Reflectiveness, Self-Certainty, Composite Index and clinical and functional variables. These included the individual items of the SOPS from the positive subscale (P1, unusual thought content/delusional ideas, P2, suspiciousness/persecutory ideas, P3, grandiosity, P4, perceptual abnormalities/hallucinations, and P5, disorganized communication), negative subscale (N1, social anhedonia, N2, avolition, N3, expression of emotion, N4, experience of emotions and self, N5, ideational richness, and N6, occupational functioning), as well as GF:S and GF:R scores. The critical p-value was set to 0.05 for the analyses of total attenuated positive and negative symptoms and Bonferonni corrected to 0.05/2=0.025 for the analyses of the GF:S and GF:R. Bonferonni correction was set to 0.05/5= 0.01 for analysis of the five individual attenuated positive symptoms and to 0.05/6= 0.008 for the six individual negative symptoms. Paired t-tests were used to evaluate change in cognitive insight from baseline to 1-month follow-up. The critical p-value was set to 0.05 for these latter analyses.

Results

Sociodemographic characteristics: Sociodemographic information and cognitive insight scores of the CHR sample are shown in Table 1.

Correlations between cognitive insight variables and attenuated positive symptoms

Correlations between cognitive insight variables and attenuated positive symptoms are shown in Table 2. No significant correlations emerged between total attenuated positive symptoms and either Self-Reflectiveness, Self-Certainty, or Composite Index scores. A trend toward higher Self-Certainty and increased severity in perceptual abnormalities/hallucinations was observed (Fig. 1), but not with Self-Reflectiveness or the Composite Index. No other significant correlations were seen between any measure of cognitive insight and symptoms severity on any of the other four individual positive symptoms.

Correlations between cognitive insight variables and negative symptoms

Table 3 displays correlations between SOPS negative symptoms and cognitive insight variables. No significant correlations emerged between total negative symptoms and either Self-Reflectiveness, Self-Certainty, or Composite Index scores. As shown in Fig. 2 & 3, a trend was observed between higher avolition and both higher Self-Reflectiveness and higher Composite Index scores, but not for Self-Certainty. No significant correlations emerged between Self-Certainty and any of the other five

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	Self-Reflectiveness	Self-Certainty	Composite Index
Total attenuated positive symptoms	0.14 (0.52)	0.13 (0.56)	0.02 (0.94)
P1: Unusual thought content/ Delusional ideas	0.18 (0.40)	0.05 (0.86)	0.10 (0.65)
P2: Suspiciousness/ Persecutory ideas	-0.01 (0.98)	-0.12 (0.57)	0.07 (0.74)
P3: Grandiosity	-0.04 (0.87)	0.20 (0.35)	-0.15 (0.49)
P4: Perceptual abnormalities/ Hallucinations	0.15 (0.48)	**0.42 (0.04)**	-0.16 (0.47)
P5: Disorganized communication	0.04 (0.87)	-0.15 (0.47)	0.12 (0.58)

Table 2: *Correlations between cognitive insight and attenuated positive symptoms. Results expressed as Pearson coefficients with corresponding p-value in brackets. Trend effects are bolded.*

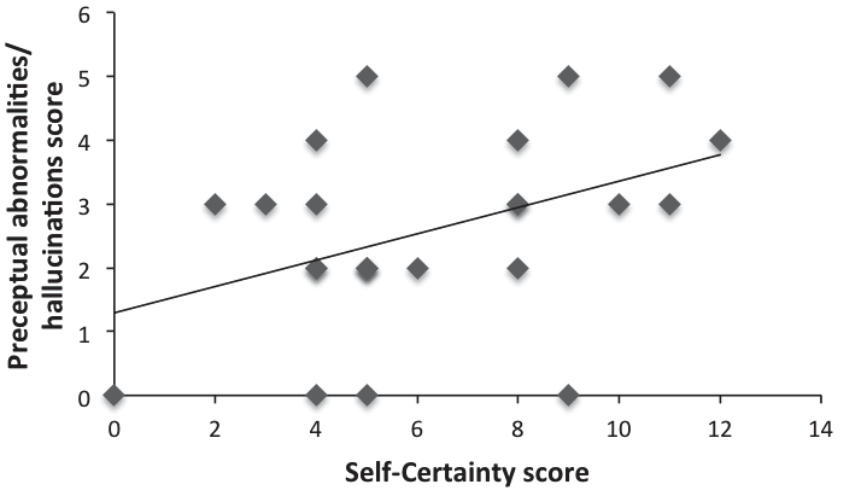

Figure 1:
Correlation between the P4, perceptual abnormalities/ hallucinations item of the Scale for Prodromal Symptoms and the Self-Certainty subscale of the Beck Cognitive Insight Scale (r = 0.42, p = 0.04).

	Self-Reflectiveness	Self-Certainty	Composite Index
Total negative symptoms	0.24 (0.25)	-0.06 (0.79)	0.20 (0.35)
N1: Social anhedonia	0.26(0.23)	0.01 (0.96)	0.17 (0.43)
N2: Avolition	**0.46 (0.03)**	-0.19 (0.39)	**0.43 (0.04)**
N3: Expression of emotion	-0.13(0.57)	-0.06 (0.77)	-0.05 (0.81)
N4: Experience of emotion	-0.23 (0.29)	0.22 (0.29)	-0.29 (0.17)
N5: Ideational richness	-0.13 (0.54)	0.04 (0.85)	-0.11 (0.60)
N6: Occupational functioning	0.18 (0.52)	-0.06 (0.80)	0.16 (0.46)

Table 3: *Correlations between cognitive insight variables and negative symptoms. Results expressed as Pearson coefficients with corresponding p-value in brackets. Trend effects are bolded.*

	Self-Reflectiveness	Self-Certainty	Composite Index
Social functioning	-0.21(0.33)	0.19 (0.38)	-0.26 (0.23)
Role functioning	-0.31 (0.14)	-0.13 (0.53)	-0.29 (0.17)

Table 4: *Correlations between cognitive insight measures and current functioning. Results expressed as Pearson coefficients with corresponding p-value in brackets.*

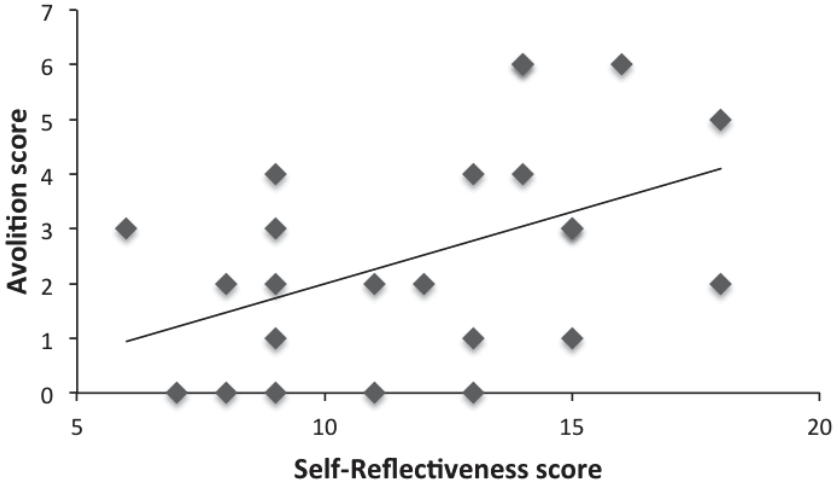

Figure 2:
Correlation between the N2, avolition item of the Scale for Prodromal Symptoms and the Self-Reflectiveness subscale of the Beck Cognitive Insight Scale (r = 0.46, p = 0.03).

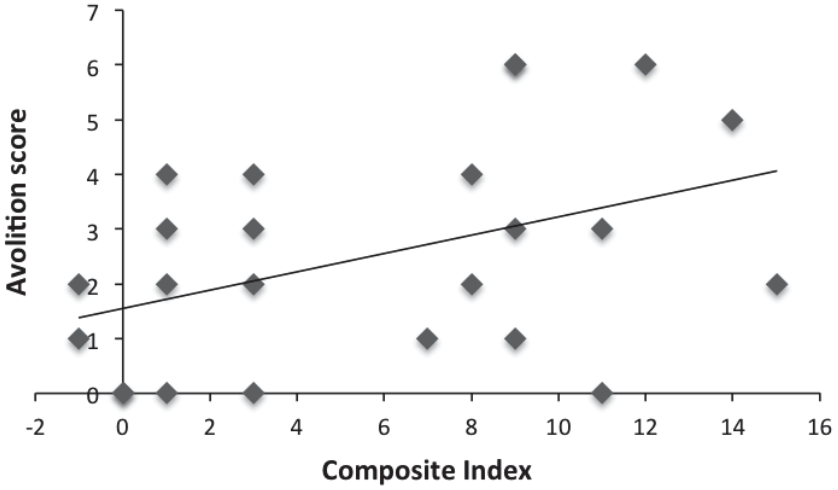

Figure 3:
Correlation between the N2, avolition item of the Scale for Prodromal Symptoms and the Composite Index (Self-Reflectiveness and Self-Certainty) (r = 0.43, p = 0.04).

	Baseline M (SD)	**1-month M (SD)**	**t-value**	**p-value**
Self-Reflectiveness	12.50 (2.62)	13.43 (3.37)	-1.19	0.26
Self-Certainty	6.07 (2.76)	6.07 (3.20)	0.00	1.00
Composite Index	6.43 (4.18)	7.36 (4.58)	-1.21	0.25

Table 5: *Paired t-Tests for cognitive insight variables at baseline and one-month follow-up (n =14).*

negative symptoms.

Correlations between cognitive insight variables and functioning

Correlations between social and role functioning ratings and cognitive insight are displayed in Table 4. Social and role functioning scores did not significantly correlate with scores on any of the three cognitive insight variables.

Longitudinal trajectory of cognitive insight from baseline to 1-month follow-up

Table 5 displays paired t-Tests for Self-Reflectiveness, Self-Certainty and Composite Index scores of a subsample of CHR participants (n= 14) who completed BCIS ratings at baseline and again at 1-month follow-up. No significant changes were observed for any cognitive insight variable between the two assessments.

Discussion

The purpose of this study was to evaluate the relationship between cognitive insight, symptom severity and current functioning, as well as the longitudinal progression of cognitive insight over 1-month, in 24 individuals at CHR of psychosis. Our results suggested a trend toward increased severity in perceptual abnormalities/ hallucinations and higher Self-Certainty. In addition, a trend was observed between increased avolition and both higher Self-Reflectiveness and Composite Index Scores. No other significant relationships were observed for any other positive or negative symptoms and any cognitive insight measure. In addition, neither social nor role functioning significantly correlated with cognitive insight in our sample. Evaluation of the trajectory of cognitive insight over 1-month indicated that cognitive insight scores remained stable over this period.

Our results indicate that greater severity of attenuated perceptual abnormalities/hallucinations was correlated at a trend level to higher Self-Certainty in our CHR sample. Although no previously published studies in either CHR or people with psychosis have reported associations between cognitive insight and hallucinations, one study in schizophrenia has reported that patients experiencing delusions and hallucinations showed a trend toward lower Self-Reflectiveness and higher Self-Certainty compared to patients with delusions and no hallucinations[19]. The two previous studies conducted in CHR samples[23,24] have not explored the relationship between perceptual abnormalities/ hallucinations and cognitive insight. The present result may suggest that hallucinations may be differentially associated with cogntive insight across multiple phases of the disease process, and may be more directly associated with aspects of Self-Certainty in CHR youth.

No significant correlations were observed between either total positive symptom scores or any other attenuated positive symptom and cognitive insight in our CHR sample. This negative finding is inconsistent with a previous study reporting that individuals at CHR of psychosis who were closer to the threshold of having persecutory ideation had higher Self-Certainty in comparison to individuals who do not meet this criteria[23]. Lower Self-Reflectiveness scores have also been reported in CHR individuals experiencing severe but not psychotic unsual thought content[23]. Furthermore, CHR individuals with near-threshold delusional symptoms had higher Self-Certainty in comparison to individuals who did not meet this criteria[24]. Overall, the results from the present study suggest a tentative relationship between hallucinations and Self-Certainty, but not for other attenuated positive symptoms including unusual thought content/delusions or total positive symptoms scores, in our CHR sample.

Analysis of the relationship between negative symptoms and cognitive insight indicated a trend toward higher avolition and higher Self-Certainty and Composite Index scores. Two previously published studies that have characterized cognitive insight in CHR did not evaluate the relationship with negative symptoms[23,24]. The current results differ from those collected in first episode psychosis patients where total negative symptom severity was associated with lower Self-Reflectiveness at a trend level of significance[17]. Higher Self-Certainty has also been reported in middle-aged schizophrenia and schizoaffective patients with greater negative symptoms severity[11]. Taken together the literature to date suggests that aspects of cognitive insight may be associated with negative symptom severity in both CHR and in schizophrenia and schizoaffective

patients.

Another novel analysis that was explored in our study was the relationship between current functioning and cognitive insight. Results of these analyses indicated no significant associations between social or role functioning and the three cognitive insight variables. This is contrary to one finding in schizophrenia patients indicating that patients with living conditions that encourage independence show greater cognitive insight compared to those who have living conditions with less independence[20]. In our study, GF:S and GF:R scales were used to measure social and role functioning. In contrast to providing two different options of living situation, social and role functioning are scalar measurements that provide an overall rating of functioning in the given area. Although the present results differ from those reported in the schizophrenia sample[20],the relationship between current functioning and cognitive insight has been understudied and therefore remains unclear.

Our longitudinal analysis of cognitive insight indicated that Self-Reflectiveness, Self-Certainty and Cognitive Insight remain stable over a 1-month time period. To our knowledge this is the first study to evaluate longitudinal change in cognitive insight in a CHR sample. That cognitive insight did not change over time could reflect a number of underlying processes, for example that Self-Reflectiveness and overconfidence are stable characteristics that may only change with changes in psychotic symptoms or functioning, among other clinical variables. In addition, brain changes that occur during adolescence may in turn change youths reasoning processes, which may be more detectable over longer periods of time such as one or two years. Although no studies have evaluated change in cognitive insight among CHR youth, one study in people with schizophrenia has reported an increase in Self-Reflectiveness and Composite Index from admission to discharge after an acute psychotic episode, but that change in positive and negative symptoms did not significantly correlate with changes in cognitive insight ratings[17]. Evaluation of change in cognitive insight over time in tandem with structural and functional brain changes that occur during adolescence and early adulthood would be particularly important for future works.

We observed in our CHR sample that participants with greater severity of perceptual abnormalities/hallucinations endorsed higher Self-Certainty at a trend level. Cognitive behavioral therapy (CBT) is one treatment that has been shown to reduce compliance behavior with command hallucinations in people with schizophrenia[28]. CBT helps individuals with psychosis become more willing to accept feedback from others and to improve their objectiveness when reflecting on distorted beliefs[29], which are cognitions tapped with the BCIS items. As such, it is possible that applying a CBT intervention in CHR individuals may help reduce distress associated with their perceptual abnormalities/hallucinations but also their cognitive insight. Interestingly, two studies have examined cognitive insight in schizophrenia before and after a CBT intervention. Granholm and colleagues[29]. These studies reported an overall improvement in cognitive insight in those who participated in a CBT intervention compared to a control group, with most improvement observed for Self-Reflectiveness [29,30]. Future treatments to promote cognitive insight in CHR may include CBT.

Our study observed a trend toward higher avolition and higher Self-Reflectiveness. In the SIPS, avolition is defined as impairment in initiation, persistence, and control of goal-directed activities. Three of the Self-Reflectiveness items require participants to reflect on their previous experiences. This may lead to the suggestion that people with low avolition may spend more time reflecting on their prior experiences rather than seeking out new ones.

Interestingly, poor social functioning, greater levels of unusual thought content and increased suspiciousness were found to be three of five predictors of conversion to psychosis in a large CHR sample[21]. That cognitive insight did not significantly correlate with any of these measures in the current study may lead to the speculation that cognitive insight may not mediate the relationship between poorer functioning, greater positive symptoms, and conversion in CHR youth. Future work in CHR converters vs. non-converters may be particularly informative in this regard.

Limitations

Limitations of the current study include the small sample size and lack of a non-clinical control group that would serve as a control group. Unfortunately, longitudinal data on changes in cognitive insight in

CHR are unavailable, and future works may evaluate cognitive insight over multiple time points to gain an understanding of its longitudinal trajectory in both clinical and non-clinical subjects. Previous studies have identified a role of neurocognition for cognitive insight in schizophrenia [5], and future works may evaluate the role of neurocognition for cognitive insight in CHR. Obtaining a larger sample size in future will help to further understand the relationship between cognitive insight, attenuated symptoms, and current functioning in a CHR sample and to test the replicability of the current findings. These future directions would be valuable in understanding the interaction between cognitive insight and multiple clinical and neurocognitive variables in youth at CHR of psychosis.

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Self-Regulation in Developing Children as Represented by Three Albertan Parenting Magazines

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Self-regulation (SR) is the ability to alter behavioral responses in response to interactions with the environment. Children who develop skills associated with high SR early in life are more prepared for school than children who fail to develop these skills. The purpose of this study was to identify the messages used to describe SR by 3 Albertan parenting magazines. An environmental scan was used to collect data from 3 Albertan parenting magazines: Apple Magazine, Calgary Childs Magazine, and Red Deer Childs Magazine published within January 2010- January 2015. A textual analysis was conducted to identify the overall SR messages presented to the public. Inductive coding was used to organize similar themes into larger categories and thereafter to determine how these Albertan media resources suggest the development of SR in children. Three themes emerged from the scan: parental role in the development of SR, disciplining children in a way that builds SR, and coping mechanisms for parents in response to tantrums. Albertan media resources describe SR in a way that is consistent with the current literature. Public resources available to parents address issues related to SR and effective management tools for parents. However, long-term consequences of early development of SR are not discussed as frequently. These results will be used to communicate with policy makers in order to develop or strengthen interventions targeted toward children who are at risk for developing poor SR. Keywords: Self-regulation: The way children control and express their emotions, attention and interactions with their environment; Early childhood development: The process of development of self-regulation in early childhood that can have positive outcomes on later growth.

Introduction

Early childhood development impacts childrens future academic success and economic productivity[1,2]. Behavior regulation or self-regulation (SR) as a component of early childhood development begins during early childhood and continues throughout adolescence. SR is a construct referring to the way children control and express their emotions, attention and interactions with their environment[3,4]. The first five years of a childs life are critical in the development of SR skills[1]. These skills develop with the maturation of the pre-frontal cortex

across the life-course and are essential for success in both school achievement and peer relations[5,6]. Developmental milestones in children, including the ability to regulate behaviors, begin at 12 months and continue until 36 months of age[7,8]. Simple SR behaviors, such as adjusting behavior and obedience to caregivers, need to be reinforced to reduce negative behavioral outcomes later in life[8].

SR Behaviors

SR occurs on a continuum where certain behaviors demonstrate strong to weak SR. Positive SR skills, for example, waiting for turns and sitting still, can develop through exposure to cognitive tasks that are age-appropriate, social interactions, and secure parent-child relationships[9,10]. According to the literature, SR development is strongly influenced by parental or care giver involvement[11]. Strong SR behaviors are reinforced through paying attention, following rules and taking turns[3]. Additionally, children who display higher levels of these skills are better engaged in school and, therefore more academically successful, and have better social competence and peer relationships[12]. For example, children who develop SR skills earlier are more likely to complete high school and college[13].Finally, children who have better academic outcomes tend to have had higher SR skills, which further supports a correlation between SR and academic outcomes[14]. In comparison, children who fail to develop early SR skills are impacted throughout their adult life and display poorer academic performance, unemployment, and delinquency[14,15].

Significance

The prevalence of children lacking SR skills is demonstrated by numerous studies[2,16,17]. For example, Rimm-Kafman, Pianta, and Cox (2000) reported nearly half of children entering kindergarten were lacking in basic SR skills such as following directions and taking turns as rated by 46% of teachers in the United States of America[18]. From an economic perspective, early intervention during childhood is cost-effective and more beneficial than corrective interventions later in life[19]. Several longitudinal studies have demonstrated the impact of early interventions[20,21]. A birth cohort of 1,037 children followed by Moffit et. al., (2011) for 32 years demonstrated significant correlations between SR and long-term effects of SR on three specific domains: 1) adult health, including substance dependence ($r=1.186$, $P=0.012$) 2) wealth, including single-parent families ($r=1.479$, $P=0.003$) and, 3) crime, including convictions ($r=1.714$, $P<0.001$)[20]. SR was assessed using reports from parents, teachers and researchers regularly throughout childhood starting at age three. Children with higher levels of SR were shown to have lower levels of substance abuse, struggled less financially, and were less likely to be convicted of a criminal offence later in life[20]. The results of their study showed that strong childhood SR had a positive, longitudinal impact on all three of these categories and highlights the importance of identifying high-risk children for the implementation of SR interventions to prevent negative outcomes later in life.

The Role of Media

Although early childhood development and SR interventions have been gaining momentum throughout North America since the 1960s, many children remain at risk for poor SR[22,23]. For example, children who grow up in economically disadvantaged homes are at a greater risk for poor academic outcomes, such as dropping out of school[24]. In order to generate public interest in early childhood development and SR, current parent perceptions and attitudes need to be determined. Mass media has been shown to play a substantial role in defining societal issues and providing health information to parents[25,26,27]. The media aims to present societal concerns in a certain way to reduce complexity and provide information for an audience to consider[25]. Media outlets can include newspapers, magazines, television, and the Internet. In fact, several studies have shown the impact of media messages promoting healthy behaviors on parent behaviour[28–32]. For example, one cross-sectional study reported 18% of parents were prompted to change a medical decision based off medical information located online[33]. Furthermore, media sources have the advantage of being easily accessible to parents and can assist parents with recognizing warning signs about behavioral problems[29,32]. Parenting magazines are particularly useful for targeting a specific population because of their placements in doctors offices[35]. These media resources are a source of knowledge and advice and often shed light on

norms of parenting experiences.

On the other hand, information distributed by the media may be inaccurate[36,37]. For example, websites often lack references and peer-review and can present conflicting descriptions of health messages[38,39]. Furthermore, Randolph and Viswanth (2004) emphasized the importance of identifying media messages already in existence because of their influence on how new information is perceived[40]. Therefore, the **purpose** of this study was to examine how three Albertan magazines framed the issue of early childhood development and SR in the last five years and whether the information is consistent with the scientific literature.

Based on the literature, SR has the potential to have both positive and negative outcomes on childrens lives. The information gained from this study will be used to determine how SR is presented to parents in a subset of Albertan parenting magazines and how parents are encouraged to translate and foster these skills to their children. This will be used to communicate with policy makers in regards to the development and modifications of current interventions in place.

This study was part of a larger study designed to identify factors related to child development and SR. The larger study collected data from the All Our Babies (AOB) cohort in order to determine predictors for SR until age 3 and will use this information to develop a screening tool. The AOB study is an established longitudinal pregnancy cohort in Alberta, Canada with data from over 3,000 pregnant women. This prospective birth cohort from Calgary, Canada used survey data from over 3,000 women to identify perinatal outcomes in women less than 35 years of age[41]. This media analysis will complement the development of the screening tool to inform knowledge mobilization and communication strategies.

Methods

An environmental scan was undertaken to understand how SR is presented to Albertan parents. Environmental scans are often used to highlight information and examine the current status of topic[42]. They involve the systematic collection of data and enable review of a diversity of information about a topic [43]. Once the scan was completed, the data was analyzed and then a composite list of themes was created from the results.

Data Collection

A scan of Albertan parenting magazines including Calgary Childs Magazine (CCM), Apple Magazine, and Red Deer Childs Magazine (RDCM) was conducted using publically available archives from the previous 5 years (January 2010-January 2015). These resources were selected because they are free, widely distributed, and readily available sources of information used by parents. The scan was restricted to the Albertan magazines printed in English published between January 2010 to January 2015. The time frame was chosen because of the time restriction of the honors project. Key words included self-regulation, and school readiness. Interchangeable synonyms were identified with the help of a librarian and also used in the scan (Table 2). The relevant articles were considered only if they discussed SR or related synonyms. For example, if the articles discussed how to prepare children for preschool, emotional or behavioral regulation, or how to cope and remedy behavioral issues or similar themes they were included. Articles were excluded if they discussed any of these themes in regards to teens or adults.

The magazines included 15 issues from Apple Magazine, 30 from CCM, and 25 from RDCM for a total of 70 magazines all-together. The magazines were chosen to reflect diversity in Albertan media as well as by readership. The magazines were all accessed electronically using the public websites and archives of the respective magazines.

A dynamic search strategy was utilized where one research student thoroughly read each article from every magazine. This was done to familiarize the researcher with the terms used by the magazines. A word search was then done to search for interchangeable words and each relevant article was read to determine the context. The scan was conducted from December 2014 to January 2015. The researcher (ZV) scanned through the individual articles, as well as the titles, and photo captions. Key words were highlighted and the article set aside for a more in depth analysis.

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Magazine	Readership	Age Group(yr)	Publishing
CCM	Excess of 150,000	25-44	6/yr ±23.5
Apple Magazine	130,000	25-65	4/yr
RDCM	No data	-	6/yr

Table 1: *Demographics of Three Albertan Parenting Magazines: Calgary Childs Magazine, Apple Magazine, and Red Deer Childs Magazine.*

Key Words	Interchangeable synonyms
Self-regulation	Behavioral problems, emotional control, tantrums, inattention
School readiness	Preschool readiness, resiliency

Table 2: *Key terms and definitions associated with SR that were used in the environmental scan, conducted between December 2014-January 2015.*

Analysis

A textual analysis was used to analyze the data[44,45]. One researcher (ZV) inductively coded the articles and debriefed with a senior research assistant (JS or HB) to identify similarities between concepts. Initial themes were developed by recording the context of each of the key words in an excel document. Once every magazine and article was read, a second reading was done on the articles containing the key words to ensure rigor. One researcher (ZV) identified similarities in themes by the context of each article and grouped them together. Once new themes stopped emerging, the number of articles in each category then determined major themes. Weekly meetings were conducted with a senior research assistant (JS) in order to incorporate feedback on organizing themes. Additionally, debriefing was used to determine which themes were shown to be of most importance in the parenting magazines. Alternative strategies to organizing data were considered as well.

Results

During the five-year period of January 2010 to January 2015, SR was specifically mentioned in only CCM in 3 issues out of the 70 issues scanned. In all 3 issues, SR was referred to as self-control. Behavioral regulation and emotional control were more commonly used to describe SR as compared to directly mentioning SR, and were used more frequently in Apple Magazine and CCM compared to RDCM. The environmental scan of parenting magazines shows Albertan media, specifically CCM, describes building emotional control and strategies for managing emotional outbursts on average 6.8 times per year. Comparatively, early childhood development and its impact on long-term consequences of SR development were mentioned only in Apple Magazine at least once per year from 2012 to 2014. Two articles were excluded from the analysis because they discussed serve and return exchanges in teens and adults. Three major themes were discovered from the data: parental role in the development of SR, disciplining children, and parental guides in response to tantrums.

Theme 1: *Parental Role in the Development of SR*

Apple Magazine focused on parental interactions to maximize cognitive development and the promotion of SR. In the Fall 2012 issue of Apple Magazine, Serve and Return described interactions that were used by parents to communicate with their children[46]. The phrase was found in 10 separate articles within Apple Magazine, and referred to exchanges between parents and children that are used to strengthen brain development[46]. These exchanges were described to promote healthy brain development in babies and children and were said to impact future mental and physical health. They included gestures and sounds that are made by the parent in response to the child, for example, smiling, signing, or talking[47]. Additionally, these relationships are essential in fostering emotional control and regulation. Early brain development was also described as having a role in emotional regulation and healthy development later in life. Two articles from Apple mentioned screen-time as a poor substitute for serve and

return interactions, and stressed the important of face-to-face interactions[48,49]. Reading to children was a common interaction suggested in all three media sources. Apple Magazine stated reading would help develop emotional and cognitive skills, while CCM also mentioned reading to children to help build skills that would prepare them from preschool[50–52]. Finally, RDCM mentioned reading to children to help develop literacy skills, and emotional intelligence for academic success[53,54].

Theme 2: *Building discipline in a way that encourages the development of SR*

The second major theme from the textual analysis was how parents should discipline children in order to foster positive development of SR. CCM described disciplining as a dynamic process that involved recognition of age, skill, ability, and experience[55]. From the 31 issues of CCM, 15 articles focused on strengthening discipline. One method described by CCM to promote effective discipline was Time ins. Similar to time-outs, time ins encouraged parents to extract children from a stressful situation so that they could reflect on their behavior. This method strives to help children regulate their behavior supportive and nurturing environment[56,57]. It was described by CCM as a strategy to calm children down and remove themselves from emotional situations. The children are encouraged to retreat to a place of their own choosing, rather than of the parents choosing to regain control of their emotions. The method is not a punishment and encourages children to focus on their emotional control so they can return to the present. Only one article from Apple Magazine described discipline, where The Positive Discipline Program (PDP) was referenced as an alternative to physical punishment[58]. Similar to the strategies proposed by CCM, The PDP encourages parents to let their children solve problems, rather than resorting to punitive methods which can include physical punishment or shaming.

Theme 3: *Tantrums*

Parents reactions to tantrums and the loss of emotional control was the third major theme. Eight articles from CCM referred to tantrums and how parents should focus their attempts to control and react to tantrums. Apple Magazine and RDCM mentioned tantrums in one article each. Apple Magazine focused more on emotional regulation rather than tantrums. For example, talking about and accepting feelings were methods cited to help childrens emotional development[59,60]. CCM also described tantrums as legitimate ways for children to express emotions. Apple Magazine, CCM and RDCM all suggested tantrums and emotional dysfunction could result as a consequence of stress[61–63]. On the other hand, CCM also suggested tantrums could be caused by a desire for the childs control, or inability to express or control their emotions[64]. Several approaches of coping with tantrums were discussed in CCM, including: offering choices, showing empathy, and preventative approaches[65]. Finally, CCM stressed the importance of avoiding child shaming in order to avoid damaging the relationship with children[56,66].

Discussion

In this study using a textual analysis, we examined how Albertan parenting magazines described SR. Parenting resources such as websites and magazines reach hundreds of thousands of viewers each month[67,68]. Another study showed 97% of mothers related to the content in parenting magazines, and 90% of mothers trusted the information[69]. Our findings showed that the information presented in three parenting magazines accurately described how parents could encourage and foster the development of strong SR skills in their children, and was consistent with the information in the literature.

Responsive Parenting

SR, as defined by the literature, is a construct referring to the way children control and express their emotions, attentions, and interactions with their environment[3,4]. The findings from this study show SR is accurately defined by a subset of Albertan parenting magazines as a form of emotional control that is influenced by parental interactions. Responsive parenting or Serve and Return interactions are predictive factors in determining childrens future emotional regulation[70]. Apple Magazine focused heavily on these Serve and Return interactions, and strongly encouraged parents to communicate in multiple forms with

their children. These interactions involve responsive parenting, where parents are encouraged to sing, talk, read, or communicate with children and have been shown to be an important contributors to emotional regulation[71]. For example, Kim and Kochanska (2012) found children who experienced responsive parenting and had better relationships with their parents had higher levels of SR[72]. Recent analyses using local Albertan data show that daily parent-child interaction in the form of reading or imitation play was protective for early developmental delay at 1 year of age (McDonald; unpublished data).

Parenting Styles

In addition to responsive parenting, parenting styles are strongly correlated to childrens development and are well documented in the literature[6,73]. There are multiple styles of parenting, as described by Baumrind (1966): authoritative, authoritarian, permissive, and rejecting/neglectful[74]. Authoritative parents are characterized by warmth, responsiveness, acceptance, and support, while authoritarian parents are less likely to use warmth and exercise the authority more strongly than authoritative parents[73]. Permissive parents are the least demanding, and show higher levels of acceptance with their children and rejecting/neglecting parents have lower warmth and responsiveness[73]. Most studies regard authoritative as being the most beneficial, although the literature shows mixed results over the development of SR and the level of control parents exercise[75,76]. Although not specifically mentioned in any of the parenting magazines, authoritative parenting was highly encouraged by Apple and CCM.

One component of authoritative parenting styles was the disciplinary tactics employed by parents. Positive discipline is method designed to build constructive, supportive relationships between parents and children. The method focuses on using alternative strategies such as encouragement, communication, and acknowledgement of positive behaviors, to discipline without resorting to punitive methods. Childrens behavioral responses and parental self-efficacy were shown to improve when parents limited punitive disciplinary tactics, and instead, used positive responses such as encouragement[77]. For example, time-outs were citied as a common strategy employed by parents, but CCM described them as an ineffective method that deals only with overt, behavioral issues, but disregards the covert, underlying issues. Furthermore, this leads to power struggles and does not effectively discipline children. Alternatively, Time-Ins are not used as punishments, but are used to help children remove themselves from a situation while experiencing heightened emotions. This procedure focuses on the needs of the child, and allows parents and children to engage in problem solving skills to deal with conflict. Consequently, children who are exposed to authoritative parenting styles are more likely to have heightened SR skills[73,78].

Emotional Breakdowns

One of the key indicators that demonstrate strong SR is being able to cope with heightened emotions. Although studies suggest that nearly 85% of preschoolers have emotional breakdowns, frequent tantrums can be indicative of developmental issues[79]. Gross et. al., (2003) showed that children who experience difficulty regulating emotions are at risk for negative outcomes later in life[77]. Conversely, Eisbach et. al., (2014) stated tantrums and emotional outbreaks are considered normal developmental processes[80]. Apple Magazine stressed the importance of role modeling and handling emotional breakdowns with tenderness and warmth, rather than reacting negatively and raising voices. Similarly, CCM also suggested the use of empathy, rather than disregarding their feelings. Therefore, parents who are emotionally supportive are at an increased likelihood of promoting SR development in their children[81]. Finally, despite the large body of research highlighting the importance of early childhood development, only Apple Magazine described the long-term impacts of building strong SR skills in children. These were only discussed in one issue per year during 2012 2014. For example, in the Fall 2012 issue, Apple mentioned that early experiences are critical in brain development and can be significant in contributing to healthy lives[82].

In summary, the information presented by the Albertan parenting magazines was consistent with the information in the literature on the impact of parental influence on the development of SR. Both have highlighted the importance of modeling and using authoritative, supportive parenting, rather than punitive methods to strengthen SR. Increasing parents knowledge of SR development

in their children and highlighting the importance of supportive strategies such as daily interaction, especially among those who are at risk for poor development, can have far-reaching effects. Increasing awareness will present parents with opportunities to address issues with SR earlier rather than later.

Limitations

Although all attempts to use the best practices of textual analysis were performed, this study was limited by several factors. The primary limitation was the time restriction enforced by the Honors class, which prevented the analysis from including more media recourses from national or internal sources. Finally, the validity of this study was threatened by having only one researcher identify themes. This was mediated by debriefing held with two senior researchers.

Conclusion

This scan of Albertan parenting magazines suggests that the freely available information for parents does include identification of SR issues and provides effective strategies to optimize development. This media analysis showed that Albertan magazines do not sufficiently highlight the importance of long-term implications of early childhood development of SR. This suggests that most Albertan parents may not be aware of the consequences of underdeveloped SR skills. Future research endeavors should focus on including more media resources such a YouTube, radio interviews, and television programs as well as increasing the scope of the scan to a national or international level. This would provide more comprehensive data on how SR is presented to the public on a larger scale. Finally, the information gathered from this study will be used to communicate with stakeholders on what information is publically available to parents, as well as how current interventions being used to build strong SR can be evaluated to meet the needs of the population. This will then be used to evaluate the current programs that are being used to promote SR to children.

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Staffing Pharmaceuticals: The Case of Novartis

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This theoretical study contributes to the research of pharmaceutical companies' HR Management practices, and more specifically their staffing systems, through close examination of Novartis Consumer Health Division's recruitment system. After an overview of the firm's overall staffing philosophy, external and internal recruitment are also reviewed. E-Recruitment is explored due to its significant place in today's staffing methods, as a result of technological advancements. Last but not least, the Equal Employment Opportunities of Novartis are examined, since Human Rights and Diversity & Inclusion receive great attention nowadays in most companies' HR Management strategies. The findings of this study for each section are based on a comparison of the information which was provided through interviews of HR Department employees of the company, as well as my individual research, with the literature review. The most important conclusions that were drawn were, first, that Novartis closely follows Schneider's Attraction-Selection-Attrition (ATA) model when it comes to its Person-Organization versus Person-Job fit, and second, that one of the main methods through which the company achieves organizational effectiveness, is through successful alignment of its HR systems with those of the other departments/line managers. Finally, recommendations for future research are also provided.

Keywords: HRM, Recruitment, Pharmaceuticals, Person-Organization vs Person-Job fit, Equal Employment Opportunities, Staffing.

Introduction

Nowadays, it is very common among CEOs to be citing their people as the resource that adds most value to the company. This is justifiable, because corporate culture, mission, vision, and performance are all dependent upon the people who form the organization, and who work together to accomplish organizational goals and objectives. It is therefore of crucial importance to choose the right people, in the right numbers, time and place. This is where recruitment comes in, to contribute to organizational effectiveness. Recruitment affects performance, turnover rates, profitability and many more organizational functions. It is therefore worthwhile to study each firm's staffing system.

Novartis AG is a Swiss multinational pharmaceutical company, founded in 1996, in Basel, Switzerland. It has a current revenue of 56.3bn CHF, while it employs about 135.000 people worldwide. Novartis is dedicated to the research, development, production and marketing of various healthcare products. At the moment, the company consists of five segments: Pharmaceuticals, Alcon

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(vision care products), Sandoz [vaccines, diagnostics, consumer health, which include over-the-counter medicines (OTC)] and Animal Health. In February 2014, the company acquired CoStim Pharmaceuticals Inc. (cancer treatment), and GSK's oncology portfolio in March 2015.

The current paper examines the Novartis Nyon Consumer Health Division staffing system, in its Swiss Headquarters, as well as in its worldwide subsidiaries. Functions such as recruitment and person-organization vs. person-job fit are addressed. Any information on Novartis' systems derives from a number of interviews I have conducted with HR specialists of the company worldwide, as well as my individual research. Conclusions on each chapter concerning Novartis' staffing system will be drawn, as a result of comparing the company's functions to the literature review.

A. Theoretical Analysis of Staffing Systems

1. Overview of the Staffing System

Staffing is defined as the system that guides the "acquisition, deployment, and retention of an organization's workforce"[1]. However recent this definition may sound, it has its roots back in ancient times. As Aristotle, the great Greek philosopher and scientist, explains:

"[t]here are four attributes which the head of the household must have to deal with his property. First, the ability to acquire. Second, the ability to preserve what is acquired: if he doesn't have that, there is no benefit in acquiring. Third, he must know how to improve his property. Fourth, how to make use of it. After all, those latter two attributes are why we want the ability to acquire and preserve"[2].

-Aristotle, *Economics,* 1344B

What Aristotle practically stresses in this passage is the significance of the notion of acquiring, developing and retaining one's workforce. The main purpose of staffing is to make sure that a company constantly possesses the appropriate quality and quantity of employees in the correct place and time, in order to effectively carry out the work of the institution. Tasks must be integrated to form a procedure which functions in a "timely fashion", and these tasks ought to be "harmoniously coordinated with the environments and contexts in which they occur"[3].

In the case of pharmaceuticals, according to Reche et.al, "[i]n the pharmaceutical industry, firms have strategies based on a strong investment in research, development and innovation, as an essential aspect for gaining and maintaining their competitive advantage. Consequently, from the perspective of SHRM [Strategic HR Management], if the firm's strategy is oriented to innovation, its HRM must seek out and execute actions in the HR area that most contribute to the success of that general corporate strategy"[4]. In other words, the point where staffing comes in the strategy of innovativeness is through the process of the firm's external recruitment. According to Reche et.al, strategic innovation in pharmaceuticals also "derives through a firm's learning programs"[4].

2. Person-Job or Person-Organization Fit?

The person-job fit is defined as the match which aligns the "characteristics of individuals and jobs in ways that will result in desired HR outcomes" [5]. In other words, there needs to be a match between the requirements of a job, and the qualifications and motivation of an individual. The qualifications of a person are called Knowledge, Skills, Abilities and Other characteristics (KSAOs). If the match between the person's KSAOs and the requirements of the job is good, hiring such a person will have several benefits for the organization, such as improved performance, retention and job satisfaction[6].

On the other hand, person-organization fit is defined as the "match of an individual's values with the value system in a specific organizational context and the potential effects that this match (or lack of a match) has on employees' behaviors and attitudes within the organization"[7]. In other words, person-organization fit refers to the congruence of an applicant's personal values, which match with those of the organization (e.g. innovation and teamwork). There is a need for employees to fit the characteristics of an organization and not just the requirements of a specific job. This is because, according to Bowen et.al, this concept is based on the notion of employing a "whole individual" who will match well with the corporate culture[8]. Furthermore, this

model focuses on that the selection should not only be based on the match of the person's KSAOs and the job's task demands (person-job fit), but also on the match between personal and organizational values (person-organization fit). The model is therefore more beneficial, because it combines both theories of selection (i.e. Person-Organization fit and Person-job fit). Furthermore, an essential aspect to which attention should be paid by the interviewer during the selection process, is to have a very clear view of the espoused and enacted values of the company, so as to fairly evaluate the applicant.

With regards to pharmaceutical companies, Pfizer, one of the world's premier biopharmaceutical companies, known for its devotion to training and developing its employees, decided to alter its staffing and development system in 2007[9]. In the past, the company used to hire people who matched the job description. However, nowadays it is extremely significant for giant biopharmaceuticals to sustain an uninterrupted flow of promising medications, in order to stay competitive and to also antagonize with smaller firms. As a result, Pfizer altered its staffing system to one in which employees are hired with the potentiality to develop and to "jump from one position to the next", explains Chris Altizer, Vice President of Global Leadership and Talent Development[10]. Therefore, it would be worth the while to examine whether Pfizer's initiative is a trend in the pharmaceutical industry overall, or just a preference of the specific company.

3. Recruitment

Inevitably, an organization must look at external sources for additional employees. According to Caruth, this is especially true when companies are "permanently expanding their workforce and innovation system"[11]. There are several benefits in external recruitment for both the applicant and the organization. As far as the applicant is concerned, Chan explains that "a successful external candidate tends to often be superior in ability relative to internally promoted colleagues and therefore enjoys a higher probability of subsequent promotion"[12]. With regards to the benefits for the organization, the latter effect is likely to "diminish up the hierarchy if external competition is more of a threat at lower job levels"[12]. Another benefit for the organization is that external candidates are people who will "bring a spark to the organization", since "by combining the experience of existing subject matter experts with new employees, we can create truly innovative products"[13]; it is also really important for an organization to be aware of the value of "next generation talent"[13].

On the other hand, in today's fast-changing technological world, e-recruitment offers a unique method of attracting talent, for both internal and external candidates. Immediacy, cost reduction and time-saving are just a few of e-recruitment's benefits, which companies are to use to their advantage. Many firms have created their own LinkedIn recruitment page, as well as relevant websites which offer applicants the opportunity to apply for any career opportunity that seems to be of interest. According to Smith, "[t]he most important part of any recruiting strategy is a career site, that not only posts your job openings, but powers them with content to really engage candidates and ensure you're finding the best talent"[14].

With regards to internal recruitment, the management in every organization needs to be aware of its current employees who are ready to move onto higher level positions, as these positions become available. According to Caruth, job postings and bidding procedures are helpful tools used in internal recruitment. On the premise that the firm retains an up-to-date basis, internal recruitment is a valid method of locating talent within the organization[15].

Last but not least, the way in which recruitment is carried out affects whether a company provides its applicants with equal employment opportunities or not. According to Caruth, "a firm must thoroughly analyze its recruiting procedures and practices"[15]. In order for this to be achieved, the author suggests that there exists a record of the continuous flow of applicants within the organization, because this will enable the firm to keep track of minority statuses, as well as job-related data concerning each applicant. In other words, such a record enables the organization to analyze the recruitment practices which affect protected classes and then modify them.

B. The Case of Novartis

After an in-depth examination of the literature review, the current section explores the staffing system of Novartis, based on the information gathered from the interviews as well as my individual research, so that

constructive criticism can follow on the next section.

Firstly, it is essential to be aware of the company's overall staffing system, in order to see the bigger picture of how Recruitment is used as a strategic partner of HR. In Novartis, according to the interviewees, the Recruitment process goes as follows: First, there is the planning and approval of a new position/replacement from both the HR Manager and the Line manager. Second, there is the search, and then the selection of the employee from the HR and the line manager. Fourth comes the preparation of a final offer from the HR. The fifth and final step is the employee's incorporation and onboarding on the program. The whole process is managed by the HR and the hiring manager through close cooperation.

Secondly, when it comes to Person-Organization versus Person-Job Fit, Novartis, like Pfizer, also seems to focus on the former, since the ability to be flexible and match the overall corporate culture seems to be of great importance to big pharmaceuticals. According to the interviewed Novartis HR personnel, they use a "Learning Agility Sustained Performance" system, which allows them to assess and predict the individuals' ability to effectively deal with first-time and changing situations (Learning Agility) and achieve superior results (Sustained Performance) over a long period of time and across different environments and contextual circumstances. These two elements are being explored throughout the recruitment process and people who had strong track of them during the past, means that they have high potentiality to adapt and develop in every kind of job. Furthermore, according to the interviewees, Novartis considers the position's requirements, but also the potential of a candidate to match the corporate values and become a future leader. To achieve this, they use a rigorous selection process and criteria based on competency and they also always work on determining the learning agility of a candidate as well.

Thirdly, Novartis' recruitment system was examined, with a special focus on external, internal, e-recruitment, and equal employment opportunities.

In Novartis, external recruitment applicants are attracted through various sources, such as employee referral, publication of advertisements in the press and on the internet, through collaboration with personnel recruitment companies etc. When it comes to choosing between open or targeted recruitment, Novartis' interviewed HR personnel explains that in the Swiss headquarters they tend to customize each search depending on the needs, whereas in some subsidiaries they use targeted recruitment for positions with high specialization (i.e. Health Economics) and open for positions where a large number of candidates is available in the market. This means that Novartis enjoys a high level of keeping up with the external environment, which further allows the company to stay innovative, which, as previously supported by Reche et.al, is the most important aspect for pharmaceuticals. A further example of how much Novartis keeps up with innovation, is the firm's relatively recent collaboration with Google (June, 2014), to produce technology contact lenses named as "smart lens", which are able to address medical conditions, such as presbyopia and diabetes. As a result, the initiative of Novartis and Google will allow people to enter into a new world of medical technological advances with unimaginable outcomes.

Furthermore, Novartis is well involved in e-recruitment, as it has its own LinkedIn recruitment page, named "Novartis Consumer Health Careers", as well as its own recruitment website, named Brassring.com. In this way, it attracts talent from all over the globe and manages to remain updated on the talent that currently exists in the market for each available position. This is of high significance for companies, because it allows for a conscious and informed view of what to expect, which, in turn, can only be beneficial for achieving organizational effectiveness through its recruiting techniques. As a result, LinkedIn, recognized Novartis as one of the "Global 100 Most in Demand Employer for 2014"[16].

On the other hand, when it comes to internal recruitment, according to the interviewees, in Novartis every time a new position arises, the company prioritizes the filling of this position internally through internal job posting. Any employee can apply, if his/her profile matches the position requirements. It is therefore understood that Novartis' internal job posting and bidding system reflects a staffing philosophy of openness and genuine interest in the advancement of its employees.

Last but not least, the company has faced some challenges with equal employment opportunities in the past, and has taken some important initiatives to deal with them. More specifically, in 2010, Novartis' United States division was charged with

a $250 million penalty for "discriminating against thousands of female sales representatives over pay, promotion and pregnancy" from the federal court in Manhattan[17]. Therefore, one of the interview questions was what practices does Novartis follow nowadays in order to avoid incidents of "glass ceiling", which is defined as "strong but invisible barriers for women and minorities to get promoted in the organization, especially in the highest levels"[18].

According to the interviewed HR personnel, in Novartis they reinforce their Equal Opportunity Policies through the opening of approximately 95% of the positions to all employees, as well as through offering annual customized development plans for all employees, aiming in preparing them for the next position. With regards to the impact that the UN Global Compact has had on the company's recruitment, the interviewees mentioned that the firm not only follows those principles but has requested them from their providers as well. On that note, the UN Global Compact requests that organizations embrace universal principles and partner, with the United Nations, as it has grown to become a critical platform for the UN to engage effectively with enlightened global business[19]. Furthermore, according to Novartis' 2012 revised Report on Diversity & Inclusion, the analogy of "board members who are not nationals of the country in which the company has its headquarters has gone up from 23% in 2006 to 32% in 2012"[20]. Moreover, in the same report, it was announced that "46% of all associates worldwide are women", whereas "42% of local managers are women, especially in the case of developing countries"[20]. With regards to the beliefs of the company's employees, Novartis conducted a worldwide survey in 2012, which resulted in that "85% believe that an inclusive corporate culture' is essential to an effectively diverse working environment"[20]. In addition, Mr. Epstein, Novartis' Division Head, explained in an interview that "[w]e want to become the best pharmaceutical company by 2016; If Novartis Pharmaceuticals has employees who all look and sound like each other, our organization will work fine, but we will never be great, and we will never do anything really revolutionary and game changing"[20].

C. Linking Theory and Practice in Novartis

The current section serves as a careful examination of the literature review and the company practices, in order to identify the links between theory and practice.

Firstly, what is understood from Novartis' overall staffing system is that it follows a very good method of strong cooperation between the HR and the line managers, and in this way it attains its organizational goals. Furthermore, Novartis seems to espouse Reche et.al's views on innovation and learning. As stated in their corporate website: "Novartis aims to change the practice of medicine, and innovation at Novartis not only means developing effective, targeted medicines quickly, but also ensuring that these medicines get to the patients who need them"[20]. With regards to learning, Novartis is the first company in its industry which managed to gain accreditation from the European Foundation for Management Development (EFMD). Novartis' Corporate Learning was praised for "the strength of its sharply focused strategic positioning and for the remarkable integration of its programs into the company's people development process"[21]. Furthermore, their learning programs were developed in close collaboration with "the world's leading minds, for example, professors from world-class institutions, such as Harvard Business School, Stanford etc."[20]. Moreover, Novartis took a unique initiative to introduce learning as a "strategic advantage", through the creation of Novartis China University and Novartis Asia University in 2009 and 2012 respectively, with the purpose of creating future leaders in emerging markets[21].

Secondly, with regards to Novartis' notion of person-organization fit, it is observed that it is intimately connected to the Attraction-Selection-Attrition (ASA) model, which was developed by Schneider in 1983[22]. Schneider supported the idea that organizations attain a one of a kind "personality," which relies on the employees who construct the firm. Schneider's model supports that certain categories of employees are drawn to specific places. The ones who match these places are unlikely to turnover, in relation to the ones who do not match. The latter forms an environment where people have comparable attitudes, experiences and beliefs, which constitute a rather homogenous

group of people. In this way, Novartis achieves its organizational goals while remaining competitive.

Thirdly, when it comes to recruitment, the firm's initiatives on their equal employment opportunities are the most interesting to examine, because they serve as an exemplary on how big pharmaceuticals deal with such challenges. What is understood from these initiatives is that Novartis has taken great care of its Equal Employment Opportunities, especially after 2010, which is evident in both the company's recent reports, as well as in its employees' survey. Besides, as the great Greek philosopher Socrates said: "[t]here is only one good, knowledge, and one evil, ignorance"[23]. This means that it is always beneficial to be aware of one's condition in order to be able to improve. The ability to be transient, to keep moving, expanding, developing and learning from past attitudes, is really important, since"[t]he secret of change is to focus all of your energy, not on fighting the old, but on building the new"[23]. The philosopher therefore concludes that "[w]e cannot live better than in seeking to become better"[23]. Novartis seems to be well aware of its strengths and weaknesses as a company, and has therefore taken some concrete steps towards the enhancement of its practices, through facing internal issues and developing employee morale and ethics, which, in turn, ensures the company's continuing future success in the following years.

Conclusion

The current paper examined the overall staffing system of Novartis Nyon Consumer Health Division. Practices concerning Novartis' external, internal and e-recruitment were evaluated as a result of comparing them with the literature review in order to offer some constructive criticism. With regards to Novartis' person-organization fit, it was concluded that the company's strategy on this issue matches Schneider's ASA model, which supports that certain categories of people are drawn to specific venues. The most significant conclusion that was drawn on how Novartis manages to achieve its organizational effectiveness, was through efficient cooperation of its HR's practice (i.e. recruitment, selection, retention, performance management) with the company's line managers. Finally, a recommendation for future research could include examining the effect of successful recruitment in the company's turnover rates in order to have a clear view of staffing's overall impact on employee retention, which is of great significance since it affects organizational effectiveness and competitiveness.

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