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Feasibility of Conducting Long-Term Follow-Up of Children and Infants Treated for CNS Tumors on the Same Cooperative Group Clinical Trial Protocol

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Conflict of interest Drs. Jennifer Hoag, Mary Jo Kupst, Marie-Eve Briere, Donald Mabbott, T. David Elkin, Jill Isenberg, Suzanne Holm, Cheryl Ambler, and Douglas R. Strother declare that they have no conflict of interest. Dr. Christine L. Trask has a family member that receives salary from Sanofi. She also has stocks in Pfizer and Sanofi.

Human and Animal Rights and Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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Abstract

Given the barriers to conducting long-term assessment of neurocognitive and psychosocial functioning of those treated in infancy for central nervous system (CNS) tumors, a multi-site feasibility study was conducted. The primary objective was to demonstrate that it is feasible to identify, locate and assess the functioning of children treated on the same protocol 10-years post-treatment. Six sites obtained institutional approval, identified and recruited subjects, and obtained comprehensive neurocognitive and psychosocial data. All feasibility objectives were met. Barriers to participation included length of time for Institutional Review Board submission and review, clinical demands, limited eligible participants at individual institutions, difficulty locating long-term subjects and stipend/reimbursement concerns. Results indicate that long-term studies are feasible and essential given the need to address long-term issues of children treated at a young age for CNS tumors, especially as they relate to later academic and vocational planning, but require significant coordination and commitment of cooperative group and institutional resources.

Keywords

Feasibility; CNS tumors; Neurocognitive; Late effects

Introduction

Children treated for central nervous system (CNS) tumors, particularly those treated with cranial irradiation and intensive chemotherapy, are at risk for development of serious neurocognitive problems (Butler & Mulhern, 2005; Maddrey et al., 2005; Moore, 2005; Mulhern, Hancock, Fairclough, & Kun, 1992; Mulhern et al., 2005; Palmer, Reddick, & Gajjar, 2007; Palmer, 2008). Since neurocognitive late effects may take years to emerge (Briere, Scott, McNall-Knapp, & Adams, 2008; Maddrey et al., 2005; Palmer et al., 2007; Palmer, 2008; Spiegler, Bouffet, Greenberg, Rutka, & Mabbott, 2004), long-term follow-up studies are essential, particularly with children diagnosed at a very young age. In this article, we briefly summarize the literature regarding the neurocognitive and psychosocial outcomes of infant CNS tumor therapy. We then turn our focus to the primary purpose of the article, which is the feasibility of conducting long-term follow-up research of children treated on the same protocol at multiple sites.

Infant CNS tumor therapy is driven by the desire to balance treatment efficacy while reducing the risk of neurocognitive adverse effects. The potential benefits of limiting the radiation dose to normal tissue have been examined, but young children appear to be particularly vulnerable to negative effects from radiation therapy (Butler & Mulhern, 2005; Lafay-Cousin et al., 2009; Merchant et al., 2004; Merchant, Conklin, Wu, Lustig, & Xiong, 2009; Moore, 2005; Palmer, 2008; Rutkowski et al., 2009). Findings indicate age at time of radiation treatment has a stronger association with decline in cognition than radiation dose (Merchant et al., 2009). Long-term effects include impairment in overall cognitive

functioning in terms of intelligence quotient (IQ), attention, memory, processing speed, executive functioning, and school performance (Butler & Mulhern, 2005; Maddrey et al., 2005; Moore, 2005; Mulhern et al., 1992, 2005; Palmer et al., 2007; Palmer, 2008).

Equally important to determine is the relationship of neurocognitive functioning after treatment to later adjustment and quality of life (QOL). While the majority of studies of psychosocial functioning in children with cancer have found low prevalence of serious problems (Noll & Kupst, 2007; Phipps, 2007), children with CNS involvement are at higher risk (Butler & Mulhern, 2005; Patenaude & Kupst, 2005; Vannatta, Gartstein, Short, & Noll, 1998; Zeltzer et al., 2009). Survivors of brain tumors treated with cranial radiation, surgery, or both are at risk for self-reported neurocognitive dysfunction, psychological distress and poor health-related QOL (Zeltzer et al., 2009). Brain tumors during childhood also are associated with greater risk for undesirable outcomes, including poorer educational attainment and employment status, lower socioeconomic achievement, and fewer interpersonal relationships (Ellenberg et al., 2009; Gurney et al., 2009; Maddrey et al., 2005).

Most treatment for pediatric cancer in North America is provided by institutions participating in clinical trials of the Children's Oncology Group (COG), the merging of the former Pediatric Oncology Group and Children's Cancer Group. Given the relatively small incidence of CNS tumors in children, individual sites typically have a limited number of children on a treatment regimen, and COG provides a unique opportunity for coordinated multi-site studies of a common treatment approach. Despite the advantages that multi-site studies offer, little has been done to examine the long-term outcomes of young children treated on the same clinical trial. When studies have provided long-term follow-up data, they acknowledge the limitation of small sample sizes several years after completion of treatment (Dhall et al., 2008). One reason for the relative lack of long-term psychosocial and neurocognitive follow-up data in children and adolescents treated at an early age for brain tumors is the relatively low survival rate of CNS tumors, particularly those diagnosed during infancy, making it difficult to accrue sufficient data at a single site. Lack of funding for reimbursement of neurocognitive testing, low recruitment and high rates of survivors lost to follow-up also limit accrual (Leisenring et al., 2009). A multi-site follow-up study of a single treatment protocol would enable us to document specific areas of functioning in this high-risk population and provide directions for targeted preventive and remedial interventions.

In POG protocol 9233/34, "A Phase III Randomized Trial of Standard vs. Dose-Intensified Chemotherapy for Children <3 Years of Age with a CNS Malignancy Treated with or without Radiation Therapy," radiation was provided only for disease progression as an attempt to lessen the impact of cranial irradiation on the neurocognitive and psychosocial functioning of infants and young children with CNS disease. Overall findings indicated intensification of chemotherapy did not provide a survival benefit to those children who received it (Strother et al., 2000); however, the neurocognitive and psychosocial outcome of these survivors had not been studied.

This feasibility study was designed to examine barriers to accrual and completion of long-term neurocognitive and psychosocial studies, and to make recommendations for larger COG-wide studies of children with brain tumors. The primary purpose was to demonstrate that it is feasible to identify, locate and assess the functioning of children with brain tumors who were treated on a single POG protocol, who, at this point, were 10–15 years post-treatment. It was hypothesized that, by developing specific strategies and procedures in collaboration with COG investigators and institutions, this aim would be achieved. While not a primary study objective, we also present basic analyses of neuropsychological outcomes from the pilot sample of children treated in infancy/toddlerhood for CNS tumors to determine if long-term outcomes trend in the same direction as predicted from existing literature.

Method

The following represent the feasibility objectives necessary to develop and implement a research strategy based on collaboration with COG-related investigators at selected sites: (1) seek and obtain funding to provide feasibility and pilot data, (2) provide continuity of the neurocognitive and psychosocial objectives of the original POG study, (3) involve relevant COG Committees and early career psychologists to ensure that study findings will be carried forward into future studies, (4) determine the appropriate research questions and relevant neurocognitive, psychosocial, and QOL measures, (5) identify eligible participating sites and participants and provide accrual data, treatment data, and outcomes, (6) develop a procedure to maximize protocol approval by local Institutional Review Boards (IRBs) and appropriately identify, locate, and contact families, (7) coordinate across participating sites to maximize conduct of the study, and (8) identify barriers and aids to successful conduct of study.

Participants

According to the COG Statistical and Data Center, 330 infants and young children, aged less than 36 months, were initially enrolled on the protocol. Among the types of tumors treated were medulloblastoma, ependymoma, atypical teratoid rhabdoid tumors, high-grade glioma, supratentorial primitive neuroectodermal tumors, and brainstem glioma. All patients were initially treated with 72 weeks of chemotherapy. Radiation therapy was prescribed upon completion of chemotherapy, or at the time of progressive disease. Radiation therapy fields and doses were dependent on diagnosis and age when treated. Of the approximately 290 patients initially eligible to receive radiation therapy on study, only 53 chose to do so. Prior to initiation of this follow-up study, 134 of these children were alive and were 10–15 years post-diagnosis; 181 (55 %) had died and 15 were lost to follow-up. The mean age of the pilot sample was 14.24 years ($SD = 1.66$). Half of the sample had undergone radiation; the other half had received chemotherapy only.

The COG Statistical and Data Center identified 51 centers with at least one eligible (alive, not lost to follow-up) participant treated on POG 9233/34. In order to be eligible to participate, sites had at least two eligible participants, the COG site principal investigator

(PI) agreed to conduct the study, and a designated psychologist or neuropsychologist was available.

Ten sites met the criterion of at least two eligible subjects and a potentially available psychologist or neuropsychologist, but three sites chose not to participate. Seven sites met all three criteria. The sites were a cross-section of geographical areas of North America. Table 1 shows the final participation for each site, with the eligible numbers as originally anticipated. In all cases, there was a higher frequency of patients who had died or were lost to follow-up than the COG data represented during the planning stages of the study. Percent participation reflects the number of living patients who participated. All but one parent and child recruited agreed to participate in the study.

Measures

Each pilot study participant completed a standardized battery of neurocognitive and psychosocial measures to examine their current level of functioning. All are widely used and considered reliable and valid within the context of research (see Appendix).

Results

Feasibility Objectives

- *Seek and obtain funding to provide feasibility and pilot data.* Funding was awarded by the National Children's Cancer Society to enable the study to provide funding for a research coordinator, limited stipends for psychologists, and testing materials.
- *Provide continuity of the neurocognitive and psychosocial objectives of the original POG study.* The psychology study coordinator and the PI from the POG 9233/34 protocol led the current study.
- *Involvement of COG Committees and early career psychologists to ensure that study findings will be carried forward into future studies.* The COG Behavioral Science Committee approved the study, while the Late Effects and CNS Committees were supportive of the project. Three of the investigators were early career psychologists or neuropsychologists.
- *Determination of the appropriate research questions and relevant neurocognitive, psychosocial, and QOL measures.* After consultation with the COG Behavioral Science group, the COG neuropsychological test battery that was developed for brain tumor protocols was selected.
- *Ability to identify eligible participating sites and participants and provide accrual data, treatment data, and outcomes (e.g. mortality, event-free survival, toxicity).* The COG Statistical and Data Center identified sites with patients treated on this protocol, as well as the number of potential patients at each site. This enabled us to contact the COG site PI, ask for their agreement to participate, and identify the designated psychologist or neuropsychologist at each center. Given that the number of lost-to-follow-

up subjects was greater than originally expected, several potentially eligible sites were eliminated, with focus on those sites with sufficient number of survivors on this protocol.

- *Development of a procedure to maximize protocol approval by local IRBs and appropriately identify, locate, and contact families.* COG procedures were utilized to protect confidentiality; unique identifiers and only de-identified data were sent to the coordinating site. The coordinating site provided templates and assistance with IRB issues. As this study did not have prior National Cancer Institute-Central IRB (NCIRB) review, some sites reported lengthy delay after IRB submission.
- *Coordination across sites to maximize conduct of the study.* Regular phone and email communications were provided by the study coordinator. Email was the most efficient mode of communication as it allowed for providing written reports, forms, and paper revisions.
- *Identify barriers and aids to successful conduct of study.* Site psychologists and neuropsychologists were surveyed regarding factors that supported or were barriers to participation, providing direction in planning for a larger scale study within COG.

Barriers and Supports to Participation

Table 2 shows the barriers to participation provided by psychologists at each eligible site, as well as supports enhancing participation in the study. In general, barriers were both individual (lack of time, conflicting demands) and institutional (IRB, lack of PI sign-on). The most common support was the presence of a dedicated psychologist/neuropsychologist in pediatric hematology/oncology who committed to conducting the study.

Neurocognitive and Psychosocial Outcomes

Table 3 shows data for diagnosis, age at time of testing, age at radiation, gender, and school class type for each of the ten subjects. Standard scores are also shown for Full Scale IQ, reading and math achievement, processing speed, and memory. *T*-scores are shown for executive functioning. The QOL total score was scored according to the PedsQL Scoring Manual (i.e., item scores transformed from 0–4 to 0–100; total score = sum of all items/number of items answered).

Table 4 shows the means and standard deviations for all of the neurocognitive and psychosocial measures for the radiated and non-radiated groups, as well as the full sample. Given the small sample size and within-group variation, statistical analyses that are more appropriate for larger sample sizes were not computed. Nevertheless, computation of effect sizes was done, as this method provides a means of determining strength of differences with small sample sizes (Durlak, 2009; Nakagawa & Cuthill, 2007). An effect size of $1.0 = 1$ standard deviation, large effects = $>.8$, medium effects = $.50-.79$, small effects = $.20-.49$ (Cohen, 1988).

From these analyses, it is clear that despite the small sample size and within-group variation, those who received radiation were much lower in IQ, processing speed, reading, arithmetic and general memory than those who did not receive radiation. In addition, children who received radiation tended to be placed in special education classes at a much higher percentage (80 vs. 0 % in the non-radiated group). Executive functioning and psychological health (based on parent report) did not differ across groups. Overall scores were within normal limits, indicating that, despite neurocognitive functioning issues, this sample did not appear to have more behavior problems than normative samples. Similarly, QOL means (based on parent and self-report) did not differ, and were similar to those of the PedsQL oncology sample (Varni, Seid, Knight, Uzark, & Szer, 2002). They were slightly, though not significantly, lower than the healthy sample.

Discussion

In this study we demonstrated that it is feasible to design and implement neurocognitive and psychosocial follow-up studies of children with CNS tumors treated on the same clinical trial protocol many years after treatment has ended—if several essential conditions are met. Having been involved with the original protocol, and with the assistance of the relevant COG resources, we were able to locate participating sites, investigators, and data on potentially eligible subjects. In addition, site investigators were able to obtain IRB approval, locate, enroll, and collect study data. Despite the small sample size, this study provides multi-site long-term outcome data on an understudied population: survivors who were treated for CNS tumors in infancy/toddlerhood who either received chemotherapy only or delayed radiation.

The pilot sample size was small ($N = 10$), with considerable variability in some outcomes, which precluded inferential statistics. However, summary data and computation of effect sizes suggested differences between those who received radiation and those who did not, with those receiving radiation much lower in neurocognitive functioning, especially IQ, processing speed, memory, and academic achievement. In contrast, the groups did not differ in emotional or behavioral health, or parent- or child-reported QOL. Given the relatively positive outcomes of the non-radiated group, assumptions could be made that radiation is the most likely factor contributing to these differences; however, we did not explore the impact of other factors, such as extent of initial tumor resection or presence of hydrocephalus.

Our findings must be considered in the context of several challenges and barriers, beginning with the subject data obtained from the COG database, which resulted in over-estimation of the number of eligible subjects at each site (due to death, loss to follow-up). Other barriers included lack of designated psychologists at potential sites or difficulty of psychologists to have time and sufficient funding to conduct the study. Another barrier was the lack of central review by the NCIRB, resulting in longer time to obtain local IRB approval. At some sites, the study may not have been viewed as high priority, given the costs (financial and staff) of opening a study for very few patients.

With the exception of very large cancer centers, the most feasible way to conduct long-term follow-up studies is through cooperative groups, such as COG. Given the relatively small

numbers in many institutions, this research would be most practical and efficient if conducted in sites with larger numbers, rather than across the entire clinical trials groups. Studies should be developed by investigators from the Behavioral Science, Late Effects, and relevant Disease Committees, and importantly, with NCIRB review. As neurocognitive and psychosocial testing involves a great deal of time and effort, it cannot be done without financial support. The psychologists in this study were dedicated and agreed to the relatively small testing stipend, but in most settings, this is not fiscally possible. Thus, it will be necessary to obtain grant funding to conduct a larger scale study. Currently, COG has implemented a funded prospective study of children undergoing treatment for medulloblastoma (ALTE07C1) that was developed with these factors in mind, and which shows significant improvement in site participation and accrual over previous neurocognitive attempts in this group. With a shortened test battery, an infrastructure for monitoring compliance with dedicated staff and psychologist participation, as well as having NCIRB approval, they were able to determine that the study was feasible to conduct (Embry et al., 2012). Such prospective studies allow for assessment over time, but the problem of maintaining an adequate sample at later assessments remains an issue. Significant cooperative group, e.g. COG, involvement is a vital component of successful long-term follow-up research, such as the current study. Utilization of COG resources, such as the NCIRB, Statistical and Data Center, and Disease Committees, in addition to funding and providing dedicated staff who can update subject enrollment at sites and provide continued contact and communication with children and families over time should allow for continuity and accrual of long-term data, but there will still be challenges as the ALTE07C1 study indicates (i.e., limited psychology support, lack of “importance” when not in therapeutic studies).

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Appendix

Measures

Each study participant completed a standardized battery of neurocognitive and psychosocial measures to examine their current level of functioning. All are widely used and considered reliable and valid within the context of research.

Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999)

The WASI is a nationally standardized measure of intelligence that can be administered to individuals as young as six years of age. Scores include a verbal, performance, and full scale IQ with a mean of 100 and standard deviation of 15.

Wechsler Intelligence Scale for Children-4th Edition, Processing Speed Index (WISC-IV PSI; Wechsler, 2003)

The PSI measures speed, accuracy, visual-motor coordination and visual scanning. Standard scores have a mean of 100 and a standard deviation of 15.

Wide Range Achievement Test 4, Reading and Arithmetic Composites (WRAT4; Wilkinson & Robertson, 2006)

The WRAT4 is a measure of fundamental academic skills, including general reading and math ability. Composite scores have a mean of 100 and a standard deviation of 15.

Children's Memory Scale (CMS; Cohen, 1997)

The CMS is a comprehensive measure of memory across the domains of verbal, visual and attention/concentration. The General Memory Index is a measure of global memory skills. Scores have a mean of 100 and a standard deviation of 15.

Conners' Continuous Performance Test II (CPT II; Conners & MHS Staff, 2002)

The CPT II is a computerized measure of sustained and selective attention and response prevention. The Overall Index has a T-score mean of 50, with a standard deviation of 10.

Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Andrews, & Peter, 2003)

The BRIEF is a parent-reported measure of executive functioning in children. Scores include a behavioral regulation index, which measures self-control; metacognition index, which measures problem-solving skills; and global composite of executive functioning. The BRIEF has a T-score mean of 50, with a standard deviation of 10.

Behavior Assessment System for Children-Second Edition (BASC-2; Reynolds & Kamphaus, 2005)

The BASC-2 is a parent-reported measure of internalizing and externalizing behavior problems. The T-score mean on the BASC-2 is 50, with a standard deviation of 10.

Pediatric Quality of Life Inventory (PedsQL; Varni, Seid, & Rode, 1999)

The health-related quality of life component of the study described in this paper was carried out using the PedsQL™, developed by Dr. James W. Varni. The current study utilized the self-reported and parent-reported Generic Core Scales, which measure physical and psychosocial (i.e., emotional, social, school) functioning. Scores range from 0–100 with higher scores indicating better quality of life (Varni, Seid, & Kurtin, 2001; Varni et al., 2002; Varni, Burwinkle, Seid, & Skarr, 2003).

Table 1

Participant sites

Centers	Potentially eligible	Deceased	Lost to follow-up	Participated	%
A	3	0	1	2	66.6
B	5	1	1	3	75.0
C	2	1	0	1	100.0
D	4	1	2	1	33.3
E	8	3	3	2	40.0
F	4	0	3 ^a	1	25.0
G	4	0	4	0	0.0
Total	30	6	14	10	41.7

% Participation = participated/(potentially eligible – deceased)

^aOne parent refused participation

Table 2

Barriers to and supports enhancing study participation

	% Sites reporting (N = 7)
Barriers	
Time to prepare for IRB submission	71.4
Busy clinical demands	42.9
Difficulty recruiting	42.9
Stipend/reimbursement concerns	28.6
Supports	
Interest in research question	42.9
Interest in future collaboration	42.9
Assistance of research coordinator	28.6
Provision of IRB/recruitment sample materials	14.3

Table 3

Neurocognitive and quality of life data by subject and group

Subjects	Diagnosis	Age (years)	Age at radiation (years)	Gender	Class types	Full Scale IQ	Reading SS	Math SS
Non-radiated group								
1	Medulloblastoma	12.6	–	Female	Regular	113	104	112
2	Mixed Mal. Neo.	12.9	–	Female	Regular	94	92	95
3	Medulloblastoma	16.7	–	Female	Regular	69	86	74
4	Ependymoma	15.8	–	Male	Regular	107	104	124
5	Ependymoma	15.8	–	Male	Regular	100	104	103
Radiated group								
6	Medulloblastoma	12.5	2.6	Female	Sp Ed	58	57	45
7	Ependymoma	12.6	4.0	Female	Sp Ed	57	46	45
8	Ana. Astrocytoma	13.8	1.3	Male	Sp Ed	69	82	55
9	Ependymoma	13.6	3.2	Female	Regular	86	91	95
10	Ependymoma	15.9	3.3	Female	Sp Ed	82	91	76
Subjects	Processing speed	Memory	Executive functioning		PedsQL total (self)	PedsQL total (parent)		
Non-radiated group								
1	133	101	50	77.17	75.00			
2	100	103	47	72.82	84.78			
3	–	–	48	66.30	–			
4	91	92	69	96.74	73.91			
5	97	96	60	83.00	68.00			
Radiated group								
6	59	28	80	26.09	52.17			
7	50	–	58	–	26.67			
8	75	34	48	90.22	60.87			
9	85	95	42	–	85.00			
10	83	43	58	84.00	78.00			

See Appendix for a description of measures. We attempted to administer all measures to each participant but in some cases not all were completed due to participant impairment, use of an alternative measure, or for unknown reasons (participants were told they could decline to answer any questions they did not want to complete)

Mixed Mal. Neo. mixed malignant neoplasm

Ana. Astrocytoma anaplastic astrocytoma

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Table 4

Summary neurocognitive and psychosocial outcomes

Measures	Radiated group	Non-radiated group	Full sample	Effect sizes
WASI				
Verbal IQ	75.2 (12.15)	98.8 (12.4)	87.0 (16.99)	2.14
Performance IQ	70.2 (14.2)	94.4 (21.48)	82.3 (21.39)	1.48
Full Scale IQ	70.4 (13.35)	96.6 (17.01)	83.5 (19.96)	1.91
WISC-IV processing speed	70.4 (15.32)	105.25 (18.88)	85.59 (24.26)	2.25
WRAT4				
Reading	73.4 (20.7)	98.0 (8.49)	85.7 (19.76)	1.73
Arithmetic	63.2 (21.82)	101.6 (18.82)	82.4 (27.91)	2.13
CMS general memory	50.0 (30.63)	98.0 (4.97)	74.0 (32.72)	2.52
CPT overall index	31.7 (24.4)	28.4 (26.94)	30.29 (23.3)	0.15
BRIEF				
BRI	55.4 (13.16)	55.4 (15.19)	55.4 (13.4)	.00
Metacognition	57.6 (15.44)	54.0 (6.67)	55.8 (11.37)	.48
Global composite	57.2 (14.46)	54.8 (9.47)	56.0 (11.6)	.21
BASC-2				
Internalizing	55.0 (20.56)	49.0 (6.71)	52.0 (14.76)	.43
Externalizing	51.8 (9.01)	55.6 (20.77)	53.70 (15.23)	.37
PedsQL (self-report)				
Physical health summary	63.54 (50.23)	82.55 (18.99)	75.42 (32.0)	.64
Psychosocial health	68.33 (28.91)	77.4 (10.38)	74.0 (17.96)	.54
Summary total score	66.77 (35.37)	79.21 (11.55)	74.54 (21.79)	.62
PedsQL (parent-report)				
Physical health summary	76.28 (20.47)	88.28 (10.33)	81.61 (17.02)	.80
Psychosocial health	60.64 (17.44)	68.74 (10.11)	64.24 (14.45)	.61
Summary total score	61.59 (24.48)	75.42 (6.96)	67.74 (19.26)	.48

See Appendix for a description of measures. An effect size of 1.0 = 1 standard deviation, large effects = $>.8$, medium effects = $.50-.79$, small effects = $.20-.49$ (Cohen, 1988)