Effects of a Taiji and Qigong Intervention on the Antibody Response to Influenza Vaccine in Older Adults

Yang Yang,*† Jay Verkuilen,* Karl S. Rosengren,*† Rachel A. Mariani,* Michael Reed,*‡ Scott A. Grubisich* and Jeffrey A. Woods*

*Department of Kinesiology and Community Health and †Department of Psychology, University of Illinois at Urbana-Champaign Urbana, IL 61801, USA
‡Center for Taiji Studies, Champaign, IL 61826, USA

Abstract: Previous studies have suggested that Taiji practice may improve immune function. This study was intended to examine whether 5 months of moderate Taiji and Qigong (TQ) practice could improve the immune response to influenza vaccine in older adults. Fifty older adults (mean age 77.2 ± 1.3 years) participated in this study (TQ N = 27; wait-list control [CON] N = 23). Baseline pre-vaccine blood samples were collected. All subjects then received the 2003–2004 influenza vaccine during the first week of the intervention. Post-vaccine blood samples were collected 3, 6 and 20 weeks post-intervention for analysis of anti-influenza hemagglutination inhibition (HI) titers. We found a significant (p < 0.05) increase in the magnitude and duration of the antibody response to influenza vaccine in TQ participants when compared to CON. The vaccination resulted in a 173, 130, and 109% increase in HI titer at 3, 6, and 20 weeks post-vaccine, respectively, in the TQ group compared to 58, 54, and 10% in CON. There was a significant between group difference at 3 and 20 weeks post-vaccine and at 20 weeks the TQ group had significantly higher titers compared to the pre-vaccine time point, whereas the CON group did not. A higher percentage of TQ subjects also responded to the influenza A strains with a protective (> 40HI) antibody response (37% TQ vs. 20% CON for the H1N1 strain and 56% TQ vs. 45% CON for the H3N2 strain), but the differences between groups were not statistically significant. Traditional TQ practice improves the antibody response to influenza vaccine in older adults, but further study is needed to determine whether the enhanced response is sufficient to provide definitive protection from influenza infection.

Keywords: Taiji; Tai Chi; Tai Ji; Qigong; Chi Kung; Influenza; Antibody; Aging; Elderly.

Correspondence to: Dr. Yang Yang, Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, Louise Freer Hall, 906 S. Goodwin Avenue, Urbana, IL 61801, USA. E-mail: yyang5@uiuc.edu
Introduction

Each year the influenza virus is responsible for an estimated 36,000 deaths and up to 150,000 hospitalizations in the US (CDC, 2004). Persons above 65 years of age are at increased risk of serious illness and death, especially those with chronic diseases (CDC, 2004; Glezen et al., 2000; Barker and Mullooly, 1980). The most effective means of influenza virus prevention is administration of the influenza vaccine. Although the vaccine is usually effective at preventing serious illness and death in young adults, a large percentage of older adults do not typically generate protective levels of antibodies to the flu vaccine (Bernstein et al., 1999; Keren et al., 1998). These realities have led to research aimed at identifying factors that can lessen influenza incidence and severity and/or improve influenza vaccine efficacy.

In recent years there has been an expanding interest in alternative and complementary therapies, although few studies have examined the impact of holistic or behavioral interventions on immune function. One popular, yet understudied therapy is Taiji (T’ai Chi), a fusion of martial arts with Daoist philosophy and meditation (Qigong) and traditional Chinese medicine (Yang and Grubisich, 2005). Many studies on older adults report that Taiji improves quality of life, flexibility, strength, cardiovascular function, pain, balance, and kinesthetic sense (Klein and Adams, 2004; Xu et al., 2005; Lu and Kuo, 2006). The use of Taiji as a behavioral intervention in older adults is particularly attractive due to age-related loss of function and problems with even moderate intensity exercise interventions. One recent study also found that a Westernized form of Taiji led to a 50% improvement in the immune response to varicella zoster virus (the shingles virus) in a small group of healthy older adults (Irwin et al., 2003). These results suggest that Taiji may alter immunity in the elderly. The purpose of this study was to determine whether traditional Taiji and Qigong practice may improve the antibody response to influenza vaccine in sedentary older adults.

Materials and Methods

Subjects

We recruited 41 subjects from a larger study examining sensory and strategic mechanisms of balance improvement afforded by a combined Taiji and Qigong (TQ) program for older adults (Yang et al., 2007). Twenty-seven of those recruited had been assigned to the TQ intervention versus only 14 in the wait-list control (CON). Due to the large difference in subject number between groups, we recruited an additional 9 CON subjects using the same inclusion and exclusion criteria as the larger study for a final distribution of 27 and 23 in the TQ and CON groups, respectively. In this sub-study, subjects were excluded if they were taking medications that altered immune responsiveness (e.g. corticosteroids or cancer therapies), or had conditions associated with immune dysfunction (e.g. severe autoimmune disorders or arthritis), neurological disorders, or had cognitive deficits as assessed by the Pfeiffer exam (Pfeiffer, 1975). All subjects completed informed consent forms approved by the University Institutional Review Board. Each subject filled out a detailed medical
history providing information about diagnosed diseases, medication use, general health problems, alcohol intake, smoking status and exercise participation. Each participant also completed the Pittsburgh Sleep Quality Index (Buysse et al., 1989) to evaluate sleep quality. With respect to this sub-study, 3 subjects dropped out of the Taiji intervention, one each at 5, 8 and 16 weeks. We were able to obtain post-vaccination blood samples from all of these subjects and included them in an intent-to-treat analysis.

Research Design and Intervention

The TQ group participated in three one-hour classes per week for 20 weeks. The control group was asked to continue routine activities for the 20 weeks. Each one-hour class consisted of equal parts Qigong and Taiji form practice. The form consisted of 7 movements distilled from the Chen Style Essential 48 movement form. The 7 movements selected focused on fundamental mobility skills: weight shifting to both sides (stepping and pivoting forward, backwards, sideways and diagonally), range of motion and coordination. They were also selected for their adaptability and accessibility. The forms were broken down into components that could be taught and practiced separately and then gradually connected by transitions until, by the fourth month, they could be performed continuously as a complete routine. The Qigong practice consisted of sitting and standing meditation. Students began with short periods of sitting. Standing was added in week 2 and times were gradually increased for both, until by the beginning of the 13th week participants were performing one 10-min sitting and two 10-min standing meditations in each one-hour class. This combination of equal parts form and Qigong reflects the traditional Chinese training curriculum. The written and oral tradition of Chinese internal arts is clear on the primacy of standing and sitting meditation in nurturing complete and efficient development of Taiji’s many benefits.

Pre-vaccine blood sampling and influenza vaccination occurred during the first week of the intervention. All subjects were vaccinated with a commercially available 2003–2004 influenza vaccine (Fluzone, Aventis-Pasteur, Swiftwater, PA) containing 15 µg of hemagglutinin from H1N1 (New Caledonia/20/99), H3N2 (Panama/2007/99), and B (Hong Kong/1434/2002) strains of the virus. Blood samples were taken 3, 6 and 20 weeks after the vaccination with the 20 weeks time point corresponding to the end of the intervention for this sub-study. Serum samples were stored frozen at −80°C for later analysis.

Antibody Titer Analysis

Once all samples were collected, they were shipped frozen to a Center for Disease Control (CDC)-affiliated reference laboratory (Hackensack Medical Center, Hackensack NJ) for blinded analysis of anti-influenza antibody titer by hemagglutination inhibition (HI) assay. Serial two-fold dilutions (e.g. 10–10,240) of participant sera were subject to HI assay performed using standard microtiter techniques, which included controls for
nonspecific HI. The appropriate A and B test antigens for HI were obtained as egg allantoic fluid (WHO Collaborating Center for Influenza, CDC, Atlanta, GA). All samples from a single subject were run in the same assay. In addition to raw antibody titer, we determined influenza vaccine efficacy as the percentage of subjects that responded to the vaccine with an antibody titer > 40 HI (at any time point post-vaccination), which is considered a titer sufficient to protect people from influenza infection (Murasko et al., 2002).

Statistics
Student’s t-tests and Chi-square tests were performed to compare treatment groups on descriptive variables and Chi-square was used to explore differences in the percentage of subjects achieving protective HI responses. In order to assess the magnitude of change in HI antibody titers over time, we used a generalized estimating equations (GEE) model for gamma-distributed responses. The dependent variable here has a strong right skew, therefore the gamma distribution is an appropriate model. GEE is widely used for the analysis of longitudinal biometric data. Diggle et al. (2002) or Hardin and Hilbe (2003) are two standard references.

We employed a within-subjects analysis, because the subjects were extremely diverse in their responses. Subjects with missing data at a single time point (n = 11) were included in intent-to-treat design. Due to low statistical power associated with the small sample size, we pooled the HI antibody responses from the three different influenza strains included in the vaccine. This pooling was done using the geometric mean, which is an appropriate method of aggregation for variables that have a multiplicative relationship.

No problems were observed during model fitting. The sample size is relatively small, so we used clustered-by-subjects bootstrapping to compute standard errors. To examine the effect in a more interpretable way, we generate predicted values for each treatment group by week, along with 99.2% confidence intervals. Ninety nine point two percent gives the Bonferroni adjustment for six time and group comparisons, corresponding to an overall alpha level of 0.05.

Results
Table 1 contains descriptive baseline information regarding the 50 participants in the intent-to-treat sample. There were no statistically significant differences in gender, weight, height, or BMI between the two groups. There was a borderline significant age difference between the two groups, with the Taiji participants about 5 years older on average than controls. The groups were also similar in that there was no difference in the number of medications they took or the number of diagnosed diseases they were afflicted with. Sleep quality as measured by the PSQI was similar as was the number of times they exercised (≥ 20 min enough to “break a sweat”) each week. Groups were also similar in their intake of vitamin supplements and alcohol (Table 1).
As prior influenza vaccination or exposure can alter pre-vaccine antibody titer and the net response to the influenza vaccine, we compared pre-vaccine HI titers between the two treatment groups. Importantly, there were no significant differences in pre-vaccine antibody titers between the Taiji and control groups (Table 1) suggesting similar vaccine or exposure histories. We queried subjects about whether they had received the previous years’ influenza vaccine (which contained identical strains to the 2003–2004 vaccine). Unfortunately, as is often the case in the elderly, 1 TQ and 3 control subjects could not remember if they had or had not received the previous years’ shot. However, there were no differences between groups in the number of subjects that reported having the previous years’ influenza vaccination (12/20 and 13/26 for control and TQ subjects, respectively; \( \chi^2 = 0.46; p = 0.56 \)).

The percentage attendance at the supervised TQ sessions over the course of the 20 weeks intervention was 80.5 ± 2.9% (range 23–96%). In questionnaires administered to the participants asking about TQ practice outside of the supervised sessions we found that the TQ group self-practiced the techniques an average of 2.8 ± 0.48 (range 0–7) times per week. The average length of a self-practice meditation session was 8.9 ± 0.2 min (range 0–30 min).

Analysis of the HI titers can be found in Fig. 1. There was a statistically significant (\( p < 0.05 \)) increase in predicted geometric mean antibody titer in the TQ when compared to the control group at the 3 and 20 weeks time points (note that the mean of the CON group falls outside the 99.2% CI). Compared to the pre-vaccine time point, vaccination of the CON group resulted in a statistically significant (\( p < 0.05 \)) 58 and 54% increase in anti-influenza HI titer at 3 and 6 weeks post-vaccine, respectively. The anti-influenza

Table 1. Baseline Comparisons between Control and Taiji Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 23)</th>
<th>Taiji (n = 27)</th>
<th>Statistic; p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/Females</td>
<td>7/16</td>
<td>6/21</td>
<td>( \chi^2 = 0.44; p = 0.54 )</td>
</tr>
<tr>
<td>Age (years)</td>
<td>74.5 ± 1.6</td>
<td>79.5 ± 1.9</td>
<td>( t = 2.0; p = 0.05 )</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.4 ± 2.0</td>
<td>63.9 ± 3.0</td>
<td>( t = 1.9; p = 0.06 )</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165 ± 1.8</td>
<td>162 ± 1.7</td>
<td>( t = 1.1; p = 0.28 )</td>
</tr>
<tr>
<td>BMI</td>
<td>26.2 ± 0.57</td>
<td>24.1 ± 1.0</td>
<td>( t = 1.7; p = 0.09 )</td>
</tr>
<tr>
<td>Diagnosed Illnesses</td>
<td>3.4 ± 0.5</td>
<td>3.2 ± 0.5</td>
<td>( t = 0.36; p = 0.72 )</td>
</tr>
<tr>
<td>Medications</td>
<td>4.0 ± 0.5</td>
<td>3.6 ± 0.5</td>
<td>( t = 0.60; p = 0.55 )</td>
</tr>
<tr>
<td>PSQI( ^1 )</td>
<td>4.7 ± 0.8</td>
<td>5.3 ± 0.6</td>
<td>( t = 0.56; p = 0.58 )</td>
</tr>
<tr>
<td>Exercise (times/week)</td>
<td>3.8 ± 0.5</td>
<td>3.9 ± 0.5</td>
<td>( t = 0.20; p = 0.84 )</td>
</tr>
<tr>
<td>Vitamin Supplements</td>
<td>18/23</td>
<td>25/27</td>
<td>( \chi^2 = 0.53; p = 0.47 )</td>
</tr>
<tr>
<td>Alcohol Intake (oz./week)</td>
<td>2.8 ± 0.9</td>
<td>1.1 ± 0.3</td>
<td>( t = 1.9; p = 0.06 )</td>
</tr>
<tr>
<td>Baseline H1N1( ^1 )</td>
<td>3.99 ± 0.28</td>
<td>3.78 ± 0.39</td>
<td>( t = 0.42; p = 0.67 )</td>
</tr>
<tr>
<td>(0–5.52)</td>
<td>(0–7.32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline H3N2( ^1 )</td>
<td>6.74 ± 0.53</td>
<td>6.0 ± 0.45</td>
<td>( t = 1.1; p = 0.28 )</td>
</tr>
<tr>
<td>(4.32–13.32)</td>
<td>(0–10.32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline B( ^1 )</td>
<td>6.00 ± 0.39</td>
<td>5.48 ± 0.48</td>
<td>( t = 0.80; p = 0.42 )</td>
</tr>
<tr>
<td>(3.32–10.32)</td>
<td>(0–10.32)</td>
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\( ^1 \)Pittsburg Sleep Quality Index; \( ^1 \)expressed as Log(2) titer.
Figure 2. Percentage of subjects that responded to the 2003–2004 influenza vaccine with a protective (e.g. \( \geq 40 \) HI) response. Despite higher percentages in the Taiji group for the influenza A strains, Chi-square analysis revealed no statistically significant differences between groups in the percentage of study participants responding with protective responses \((p = 0.21, 0.47, \text{ and } 0.96 \text{ for } H1N1, H3N2 \text{ and } B \text{ strains, respectively})\).
titer at 20 weeks post-vaccine (~ 10% increase) was not significantly different from the pre-vaccine time. This is in contrast to the statistically significant (p < 0.05) 173, 130, and 109% increases relative to pre-vaccine at 3, 6, and 20 weeks post-vaccination, respectively, in the TQ group (Fig. 1). We found no significant correlations between attendance or self-reported self-practice and maximal post-vaccination antibody responses (r’s = 0.01–0.3, p > 0.05), however our sample size is quite low for an analysis of this type. Moreover, attendance at the sessions was relatively homogenous among the participants. Only one subject (23% attendance rate) was below 65%, with the majority of participants attending > 80% of the supervised sessions.

Another way to examine influenza vaccine efficacy is to determine the percentage of people who developed a protective response (e.g. ≥ 40 HI) after vaccination (Goodeve et al., 1983). As can be seen in the Fig. 2, while more Taiji participants had a protective (e.g. ≥ 40 HI in response to the vaccine) titer response, particularly for the influenza A strains, this was not statistically significant via Chi-square analysis (p = 0.21, 0.47, and 0.96 for H1N1, H3N2 and B strains, respectively).

Discussion

This is the first study to examine the influence of a Taiji/Qigong intervention on the response to influenza vaccine in older adults. Influenza is a major problem for this population because of age-related immunodysregulation that contributes to increased susceptibility, longer recovery, and failure to become adequately immunized when given the influenza vaccine (Murasko et al., 2002). Many strategies have been employed to improve influenza vaccine efficacy in the elderly. In this study, we found that 5 months of an easily performed behavioral Taiji and Qigong intervention could improve the magnitude and duration of the HI anti-influenza antibody titer response in a small cohort of older adults. Unfortunately, while there was a statistically significant increase in the amount of anti-influenza antibody produced in response to the vaccine in the Taiji group when compared to controls, the intervention failed to stimulate antibody production above a critical level (e.g. ≥ 40 HI) needed for protection against influenza infection (Goodeve et al., 1983). Although there were some differences across the vaccine strains, there was a tendency for the intervention to increase the percentage of people exhibiting a protective titer > 40 HI, although this was not statistically significant.

There are a few limitations to this study that are noteworthy. First, this was intended as a proof of concept study and was not a true randomized controlled trial. We were unsuccessful in recruiting enough control subjects (n = 14) from the larger parent trial to effectively compare the efficacy of the intervention (n = 27) on influenza vaccine responses. As such, we recruited additional subjects (n = 9) to the wait-list control group in a non-randomized fashion. We made every attempt to make sure that these subjects were similar to the parent trial by using the same inclusion/exclusion criteria. Our results indicated that on most variables (e.g. gender, BMI, number of medications, diagnosed diseases, exercise participation, vitamin and alcohol use) the two groups were comparable. The only
borderline significant (p = 0.05) difference was in age. The TQ group was on average 5.5 years older than the control group. However, older age results in reduced influenza vaccine responsiveness (Murasko et al., 2002), suggesting a possible underestimation the TQ effects reported in the current study. A second limitation of the present study was our lack of an attention control group. This limited our ability to determine whether the increase in antibody titer seen in the TQ group was due to the behavioral Taiji intervention or socialization into the study. Third, while we made every attempt to ascertain each participant’s previous year’s (2002–2003; which was identical to the 2003–2004 vaccine used in the current study) influenza vaccine exposure, a few of our subjects could not recall whether they had or had not received that vaccine. In the 92% who could recall, there were no significant differences in the percentage receiving the vaccine in the TQ (50%) when compared to the controls (60%). We also found no differences in baseline titers to any of the strains (Table 1) and, importantly, our statistical model adjusted baselines between the groups to examine relative change over time. Thus, we are confident that group differences in the response to the influenza vaccine used in this study was due to factors other than prior exposure. Lastly, while anti-influenza antibodies generated in response to vaccine are important in influenza prevention, cell-mediated immune responses also play a role (Murasko et al., 2002). Indeed, a recent study suggests that T cell-mediated responses mounted in response to the influenza vaccine may be more predictive of vaccine protection in the elderly when compared to antibody responses (McElhaney et al., 2006). We did not assess the cell-mediated immune response to the vaccine in the present study. Despite these limitations, studies such as this one provide evidence for mind-body interactions and demonstrate the utility of such behavioral interventions as complementary therapy for those whose immune systems operate sub-optimally. Clearly there needs to be a large, randomized controlled trial on TQ intervention and vaccine efficacy in this at-risk population.

There have been some studies that have examined the effects of Taiji and Qigong on immune function in various populations. Unfortunately, few of these studies have included clinically relevant measures of immunocompetence and several are inadequately controlled. For example, Manzaneque et al. (2004) found that one month of Qigong training lowered total leukocyte, eosinophil, monocyte and complement C3 levels. Jones (2002) found that 14 weeks of Guolin Qigong increased the IFN-γ: IL-10 ratio in leukocytes cultured with phytohemagglutinin in vitro. The lack of a control group in this study made it difficult to assess the contribution of the intervention. Moreover, simple measures of leukocyte counts or ex vivo cytokine production in response to polyclonal stimulation have little clinical relevance. In one carefully controlled clinically relevant trial, Irwin et al. (2003) found that 15 weeks of a Westernized version of Taiji significantly increase varicella zoster virus specific immunity in men and women over aged 60. Also, it has been found that Qigong trained subjects mounted better responses to delayed-type hypersensitivity (DTH) recall antigens when compared to controls (Ryu et al., 1995). The latter is clinically relevant because low DTH responses have been found to be related to higher mortality due to sepsis (Christou et al., 1989). Although not Taiji, mindfulness meditation techniques have resulted in improved antibody titers to influenza vaccine in a group of younger subjects.
(Davidson et al., 2003). Recent evidence also suggests that physical exercise can improve the antibody response to influenza vaccination in previously sedentary elderly (Kohut et al., 2005). This effect was mediated, in part, by improvements in psychosocial factors (Silva and Cignolini, 2005; Lee et al., 2006), which unfortunately we did not assess in the present study.

While the underlying mechanisms behind behavioral intervention’s beneficial effects on immune responsiveness in some studies remains unclear, it is well-known that there exists established links between behavior and neuroendocrine factors that can impact immune cells. For example, immune cells express adrenergic and cholinergic receptors and catecholamines and acetylcholine have profound effects on their functions (Sanders and Straub, 2002; Wang, 2004). Interestingly, Taiji has been found to enhance vagal modulation and shift the sympathovagal balance towards a reduction in sympathetic tone (Lu, 2003). Whether changes in autonomic balance in response to behavioral interventions like Taiji are responsible for altered immune responsiveness to challenge is unknown, but testable. This is the first study adopting a traditional curriculum of Qigong meditation and Taiji form practice to examine the effect of Taiji on older adults’ immune function. It would be useful in future studies to examine the effects of each of the three components of traditional Taiji curriculum (Qigong, form, and push-hands) and also to use them in different combinations. It would be also important to study the effects of static (standing and sitting) and dynamic Qigong separately and the combined.

In summary, we have found that 20 weeks of Taiji and Qigong exercise can increase the antibody response to influenza vaccine in older adults. Unfortunately, the intervention failed to increase antibody titers above the well-established protective level (> 40 HI), however a higher percentage of TQ subjects did respond favorably to the influenza A strains in the vaccine. Our results provide “proof-of-concept” and suggest that there needs to be a larger dedicated intervention trial with Taiji to definitively determine whether this type of behavioral intervention can improve influenza vaccine efficacy in older adults.

References


