INTRODUCTION
Falls are a common geriatric syndrome, with approximately 30% of community dwelling seniors experiencing one or more per year. Experts consider falls to be non-random events (Grimley-Evans, 1990) and reliable risk factors for falls have been identified. Broadly, falls risk factors can be divided into two distinct categories: (1) physical risk factors, or (2) cognitive risk factors. Physical risk factors include mobility and balance issues, which can be assessed using multiple physiological components (Lord et al., 2003). Cognitive dysfunction is also a key falls risk factor (Tinetti et al., 1988). Within the multiple domains of cognitive function, impaired executive functioning – the ability to concentrate, to attend selectively, to plan and strategize – is associated with falls (Lundin-Olsson et al., 1997; Rapport et al., 1998; Anstey et al., 2006). More specifically, the executive cognitive processes of response inhibition, as measured by the Stroop Color-Word test (Lord and Fitzpatrick, 2001; Liu-Ambrose et al., 2008a), and set-shifting, as measured by the Trail Making test (Corrigan and Hunkeldey, 1987), appear to be most relevant to falls.

It is well-known that both physical and cognitive abilities have neural concomitants, suggesting that altered functional brain responses may play a prominent role in falls risk. This hypothesis is substantiated by recent neuroimaging evidence demonstrating neural differences between fallers and non-fallers. Specifically, we previously demonstrated that the posterior lobe of the right cerebellum had significantly reduced hemodynamic response among seniors with a recent history of falls compared with non-fallers while performing the Eriksen Flanker task – a task requiring selective attention and conflict resolution – as assessed by fMRI (Liu-Ambrose et al., 2008b). Additionally, in a study examining the relationship between functional activation and physiological falls risk, we found significant associations between the left fronto-orbital cortex extending towards the insula, and the paracingulate gyrus extending towards the anterior cingulate gyrus with change in physiological falls risk over a 12-month period (Nagamatsu et al., 2011a). Taken together, these studies provide evidence that altered brain function may be associated with falls.

In our previous study (Liu-Ambrose et al., 2008b), we compared functional activation on the Flanker task between fallers and non-fallers as the difference between incongruent and congruent trials. In other words, we examined areas that showed greater activation during incongruent trials – the more cognitively difficult condition – using congruent trials as a baseline. Given our previous methodology, it remains unclear whether there are overall differences in level of blood-oxygen-level dependent (BOLD) signal in fallers relative to non-fallers, as well as the independent contribution of each type of condition (congruent and incongruent) to the results we obtained. For example, was our observed difference due to lower activation of incongruent trials or higher activation of congruent trials in fallers? This is currently unknown because we previously only examined the difference score between conditions, rather than directly comparing percent signal change between groups. Of relevance for our current study, the two different trial types engage separate cognitive processes. In particular, incongruent trials require the engagement of selective attention and response inhibition; notably, these are key executive functions that have been tied to falls (Lord and Fitzpatrick, 2001; Holtzer et al., 2007). Therefore,
examining differences in activation within each condition separately could provide valuable information regarding the specific neural correlates that contribute to cognitive alterations in fallers.

The main purpose of this 2-month prospective observational study was to examine the independent contributions of congruent and incongruent trial types on the hemodynamic response in older women with and without a recent history of falls. We hypothesized that we would observe differences in the BOLD response between fallers and non-fallers as a function of trial type. Such results would have the potential to inform us about the specific underlying neural differences that may contribute to impaired executive cognitive processing, and falls in older adults.

MATERIALS AND METHODS

PARTICIPANTS

Our sample consisted of a subset of 83 women out of 158 participants in a 12-month randomized controlled trial (RCT) of resistance training with three experimental groups: balance and tone exercises, once weekly resistance training, and twice weekly resistance training (Liu-Ambrose et al., 2009). The subset was selected based on MRI scanning eligibility and consent. Participants in the RCT included community-dwelling women who: (1) were aged 65–75 years; (2) obtained a score ≥24 on the Mini Mental Status Examination (MMSE); and (3) had a visual acuity of at least 20/40, with or without corrective lenses. Participants were excluded if they: (1) had a diagnosed neurodegenerative disease and/or stroke; (2) were taking psychotropic drugs; (3) did not speak and understand English; (4) had moderate to significant impairment with activities of daily living, as determined by interview; (5) were taking cholinesterase inhibitors within the last 12 months; (6) were taking anti-depressants within the last 6 months; or (7) were on estrogen replacement therapy within the last 12 months. Data reported here are from the baseline assessments of the trial. This study was approved by the Vancouver Coastal Health Research Institute and the University of British Columbia’s Clinical Research Ethics Board. All participants provided written informed consent.

TWO-MONTH OBSERVATION PERIOD

Falls were assessed during a 2-month observation period. During the observation period, participants completed baseline assessments, which were randomly allocated into their exercise groups, and underwent an orientation for training. Falls were defined as “unintentionally coming to the ground or some lower level other than as a consequence of sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in stroke or an epileptic seizure” (Kellogg International Work Group, 1987). Falls were recorded within the 2-month observation period using calendars that were completed daily and submitted monthly. Participants were instructed to record falls or absence of falls daily on the calendar; they were instructed that if they fell, they were to phone the research coordinator at their earliest convenience. The research coordinator noted the details of all falls reported, such as the specific circumstances and whether or not any injuries were sustained.

IMAGING

PRIMARY OUTCOME MEASURE: FUNCTIONAL MAGNETIC RESONANCE IMAGING

Brain activation was examined using functional magnetic resonance imaging (fMRI). Functional MRI is a non-invasive neuroimaging technique, which measures the BOLD signal in the brain, enabling us to make inferences regarding regional activation during performance of a cognitive task. We collected baseline fMRI data from all 83 participants with a 3.0T Intera Achieva MRI scanner (Philips Medical Systems Canada, Markham, ON, Canada) in the UBC High Field MRI Centre at the UBC Hospital.

Cognitive task parameters

The experiment was a slow event-related design. During scanning, participants performed a modified Eriksen Flanker task (Figure 1). On each trial participants viewed a visual display that contained five arrows and were required to indicate the direction...
NeuroImages (AFNI) software (Cox, 1996). Time-series images were interpolated to volumes with 1 mm³ voxels, co-registered, converted to Talairach stereotactic coordinate space, and blurred using a 4 mm Gaussian full-width half-maximum filter to compensate for inter-subject variability in anatomic and functional anatomy. Data were converted to percent signal change by time of repetition (TR). Activation foci were delineated using the Talairach atlas for the cerebral cortex (Talairach and Tournoux, 1988) and the Schmahmann atlas for the cerebellum (Schmahmann et al., 1999, 2000).

**Statistical analyses**

The primary behavioral outcome was interference on the Flanker task, which reflects reaction time on incongruent trials unbiased by differences in base reaction time. Interference was computed as the percent increase in reaction time to incongruent stimuli, over and above the average reaction time to congruent stimuli [(incongruent reaction time – congruent reaction time)/congruent reaction time] × 100 (Colcombe et al., 2004). Only correct responses are included in analysis.

For our fMRI data, we conducted a mixed-model analysis of variance (ANOVA). Specifically, to illustrate the overall effect of our experimental manipulations we tested the Group (fallers versus non-fallers) by Condition (congruent versus incongruent) interaction. To reduce the likelihood of false positives, the threshold for statistical significance was set at a p value of 0.05 (critical F = 9.05) and a minimum cluster size of 200 contiguous voxels was employed (Forman et al., 1995).

**RESULTS**

**PARTICIPANTS**

During the 2-month observation period, 14 out of 83 participants fell, resulting in a total of 15 falls. One of the 15 falls resulted in a hip fracture; eight caused moderate injuries (e.g., sprains and bruises). To create equal group sizes for statistical purposes, 14 of the remaining non-fallers were randomly selected using a random number generator in Microsoft Office (Excel) to comprise the “non-fallers” group. Demographic information for our participants is provided in Table 1. Fallers and non-fallers did not significantly differ on age, MMSE score, history of falls over the past 12 months, or TUG Test (all p's > 0.10). There was a trend towards higher physiological falls risk for fallers compared with non-fallers, F(20) = 1.96, p = 0.06.

**BEHAVIOR**

Behavioral performance on the Flanker task was not significantly different between fallers and non-fallers (p = 0.17). However, there was a trend towards fallers performing better (i.e., less interference) than non-fallers (mean interference = 18.16, SD = 10.87 and 26.30, SD = 18.47 for fallers and non-fallers, respectively), which is consistent with our previous study (Liu-Ambrose et al., 2008b). Overall, accuracy was very high on the Flanker task (mean accuracy = 97.50%, SD = 10.87). There were no significant between-group differences in task accuracy, p = 0.33.
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Table 1 | Descriptive measures.

| Variable                      | Fallers n = 14 | Non-fallers n = 14 |
|-------------------------------|----------------|-------------------|
| Age (year)                    | 69.36 (2.95)   | 68.86 (2.96)      |
| MMSE Score (max. 30 pts)      | 29.00 (0.88)   | 28.43 (0.94)      |
| Education (No, %)             |                |                   |
| Less than Grade 9             | 0 (0.0)        | 0 (0.0)           |
| Grades 9–12 without Certificate or Diploma | 2 (14.3) | 0 (0.0) |
| High School Certificate or Diploma | 1 (7.1) | 2 (14.3) |
| Trades or Professional Certificate or Diploma | 1 (7.1) | 2 (14.3) |
| University Certificate or Diploma | 1 (7.1) | 2 (14.3) |
| University Degree             | 9 (64.3)       | 6 (42.9)          |
| Number of Falls in the past 12 months | 0.71 (1.07) | 0.29 (0.47)      |
| Timed Up and Go Test (s)      | 6.70 (1.38)    | 6.14 (0.74)       |
| PPA Score                     | 0.58 (0.57)    | 0.08 (0.78)       |

FUNCTIONAL MAGNETIC RESONANCE IMAGING

Brain regions with significant activation as identified by a significant Group by Condition interaction ($F = 9.05, p = 0.01$) and their corresponding percent signal changes are shown in Table 2. There were 15 significantly active regions, including bilateral middle and superior frontal gyri, left inferior gyrus, and right superior temporal gyrus. To examine the pattern of results underlying each of the listed 15 interactions, we extracted the percent signal change of the BOLD response separately as a function of Group and Condition.

Table 2 | Regions of interest and percent signal change for the significant group by condition interaction.

| Hemisphere | Area                        | Talairach coordinates | Brodmann area | Congruent | Incongruent | Congruent | Incongruent |
|------------|-----------------------------|------------------------|--------------|-----------|-------------|-----------|-------------|
| R          | Medial frontal gyrus        | 5.9 63.5 14.1 10       | 0.1155       | 0.0706    | 1.8630     | 1.3347    |
| L          | Lentiform nucleus (putamen) | -25.2 -16.3 14.1      | 0.3583       | 0.3498    | 1.0867     | 1.1731    |
| R          | Cingulate gyrus             | 176 16.5 30.9 32      | 0.1711       | -0.3741   | 0.8963     | 0.9637    |
| L          | Inferior frontal gyrus      | -43.6 16.7 -10.2 47   | 0.1623       | 0.2403    | 0.2746     | 0.3873    |
| R          | Middle frontal gyrus        | 32.4 38.5 39.2 6      | 0.6656       | 0.7138    | 2.2816     | 1.9767    |
| L          | Middle frontal gyrus        | 38.6 65.9 16.5 10     | 0.3473       | 0.4817    | 1.1410     | 1.0090    |
| L          | Subcallosal gyrus           | -2.7 18.0 -14.4 25    | 0.4460       | 0.3236    | 2.1828     | 1.7486    |
| L          | Middle frontal gyrus        | -51.1 14.7 29.0 9     | 0.3503       | 0.2264    | 1.5866     | 1.3446    |
| L          | Middle frontal gyrus        | -21.9 -1.8 59.9 6    | 0.3969       | 0.3815    | 1.2027     | 1.3181    |
| L          | Parahippocampal gyrus       | -40.1 -40.7 -6.1 19   | -0.4506      | -0.4822   | 0.5950     | 0.2896    |
| R          | Medial frontal gyrus        | -4.2 -118 53.9 6     | 0.7175       | 1.0006    | 2.3380     | 2.0153    |
| R          | Superior temporal gyrus     | 44.8 -39.6 12.8 41   | -0.3750      | -0.2965   | 0.5511     | 0.2110    |
| L          | Superior frontal gyrus      | -21.8 59.4 -13.1 11  | 0.5451       | 0.5765    | 2.5699     | 2.1962    |
| R          | Superior frontal gyrus      | 13.3 43.2 44.7 8     | 0.1350       | 0.1018    | 0.7845     | 0.3352    |
| L          | Posterior cingulate         | -178 -42.3 9.5 29    | 0.0456       | 0.0197    | -0.0784    | -0.2366   |

DISCUSSION

Our study aimed to examine differences in hemodynamic response between senior fallers and non-fallers as a function of condition type during the Flanker task. In this regard, we report two key findings. First, fallers had a smaller difference in functional activation between congruent and incongruent trials relative to non-fallers. Second, fallers overall had a reduced level of functional activation compared with non-fallers. Taken together, our results align with the current prevailing notion that executive cognitive functions play a critical role in falls risk in older adults and bring to light several noteworthy points of discussion.

First, our results are consistent with previous reports that fallers have superior performance on the Flanker task relative to non-fallers (Liu-Ambrose et al., 2008b). While behavioral performance on the Flanker task in our current study was not significantly different between fallers and non-fallers, fallers did manifest a behavioral response pattern that was indicative of less interference from the flanking distractors, compared with the non-fallers. This has been interpreted as an overly narrow focus of spatial attention in fallers. Briefly put, studies in healthy young adults have demonstrated not only that the size of the attentional spotlight is flexible (Eriksen and St James, 1986), but also that the spotlight becomes more narrow and focused under conditions of high perceptual load (Handy and Mangun, 2000; Handy et al., 2001).
Thus, within this context, our behavioral results suggest that fallers may have reduced attentional sensitivity in parafoveal vision and that this spotlight narrowing may be associated with deficits in visual-perceptual processing. This theory is corroborated by our neuroimaging results showing a negligible difference in percent signal change between incongruent and congruent trials in fallers. Specifically, that the stimuli are being processed similarly in the two conditions suggests that fallers may not be cognitively evaluating the peripheral arrows to the same extent as non-fallers.

Second, what might account for the overall reduction in the BOLD signal in fallers compared with non-fallers? This pattern of results could be the consequence of decreased neural function and/or structural integrity of the brain. In particular, neural changes inherent to pathological aging can alter neurovascular coupling, which is responsible for the BOLD response (D’Esposito et al., 2003). Functional activation has also been shown to be more distributed throughout the brain as a compensatory response to combat reduced processing capacity at local brain regions in order to maintain task performance (Cabeza, 2002). While this possibility is speculative at this point, changes in the distribution of activation between fallers and non-fallers is plausible; indeed, the idea that fallers may exhibit altered within- and between-network connectivity is something that is currently being examined (Hsieh et al., in submission).

An alternative explanation for our results is that fallers might not have been paying as much attention to the task overall compared to non-fallers – thus resulting in an overall lower BOLD response. Indeed, previous research has pointed towards an association between attentional deficits and falls (Nagamatsu et al., 2009, 2013). We highlight, however, that we did not observe between-group differences on task accuracy during the Flanker task. Given that fallers demonstrated equivalent performance to non-fallers suggests that their level of attention was similar; therefore, our current data does not allude to the notion that a lack of attention in fallers is contributing to the reduced BOLD response. Additional research is necessary to further investigate the difference in BOLD response between fallers and non-fallers.

Finally, one specific region that we found to exhibit reduced activation in fallers compared with non-fallers – the right medial frontal gyrus (BA 10) – is of particular interest, due to its identified role as a “gateway,” functioning as a higher-level control mechanism to facilitate attentional orienting towards stimulus-related versus stimulus-independent thoughts (Burgess et al., 2007a,b; Smallwood et al., 2012). In particular, BA 10 has been implicated in self-generated thoughts pertinent for planning, reasoning, and engaging working memory (Christoff et al., 2003). Furthermore, a study by Boyd et al. (2009), found that activation in BA 10 was critical for planning goal-directed movements during a manual task. Importantly, such functions are essential for safe mobility and corroborate past evidence that older adults at-risk for falls demonstrate poor decision-making and judgments when crossing a stimulated virtual street (Nagamatsu et al., 2011b). Hence, future work should focus on examining the specific role of BA 10 and motor planning in fallers.

We acknowledge the limitations of our study. Our sample size is small and limited to women aged 65–75 years. Hence, future studies examining the relationship between falls and executive cognitive functioning should investigate whether such effects extend to a larger and more heterogeneous sample. Lastly, the cross-sectional nature of our study limits us to conclusions regarding the correlational associations between functional brain activation and falls status, rather than providing evidence for causal relationships.
Future work examining the distribution of activation in the brain during an executive cognitive task in fallers is warranted.

In conclusion, our study is the first to provide evidence that older women with a history of falls exhibit a smaller difference during an executive cognitive task. Generally, future work aimed at identifying underlying brain structure and function responsible for impaired cognitive processing in older adults at-risk for falls will augment our current understanding of the mechanisms underlying falls – and aid prevention and treatment efforts.

ACKNOWLEDGMENTS

Lindsay S. Nagamatsu is a trainer with the Natural and Sciences and Engineering Research Council of Canada (NSERC). Funding for this study was provided by a British Columbia Network of Aging Research (BCNAR) seed grant to Lara A. Boyd and Teresa Liu-Ambrose and M0R-93373 from the Canadian Institute of Health Research (CHIR) to Teresa Liu-Ambrose. Teresa Liu-Ambrose is a Canada Research Chair in Physical Activity, Mobility, and Exercise Neuroscience.

AUTHOR CONTRIBUTIONS

All authors contributed to study concept. In addition, Lindsay S. Nagamatsu was responsible for data collection, data analysis and interpretation, and manuscript preparation. Lara A. Boyd was responsible for data analysis and interpretation and critical review of the manuscript. Chun Liang Hsu was responsible for data collection and critical review of the manuscript. Todd C. Handy was responsible for data interpretation and critical review of the manuscript. Teresa Liu-Ambrose is responsible for data collection, data interpretation, and manuscript preparation.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 08 September 2013; paper pending published: 15 October 2013; accepted: 24 November 2013; published online: 19 December 2013.

Citation: Nagamatsu LS, Boyd LA, Hsu CL, Handy TC and Liu-Ambrose T (2013) Overall reductions in functional brain activation are associated with falls in older adults: an fMRI study. Front. Aging Neurosci. 5:91. doi: 10.3389/fnagi.2013.00091

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