

Heart rate reactivity is associated with future cognitive ability and cognitive change in a large community sample.

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1 Heart rate reactivity is associated with future cognitive ability and cognitive
2 change in a large community sample

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8 Running title: Reactivity and cognitive ability

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1

2 **Abstract**

3 The relationship between cardiovascular reactions to acute mental challenge in the
4 laboratory and cognitive ability has received scant attention. The present study examined the
5 association between reactivity and future cognitive ability. Heart rate and blood pressure
6 reactions to a mental stress task were measured in 1647 participants comprising three distinct
7 age cohorts. Cognitive ability was assessed using the Alice Heim-4 test of general
8 intelligence and choice reaction time five and 12 years later. High heart rate reactivity was
9 related to higher general intelligence scores and faster choice reaction times at both follow-
10 ups. High heart rate reactivity was also associated with a smaller decline in cognitive ability
11 between assessments. These associations were still evident following adjustment for a wide
12 range of potentially confounding variables. The present results are consistent with the notion
13 that high reactivity may not always be a maladaptive response and that low or blunted
14 reactivity may also have negative corollaries.

15

16 *Keywords:* Blood pressure, cognitive ability, cognitive change, heart rate, reactivity

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1 **1. Introduction**

2 Little is known about the association between cardiovascular stress reactivity and
3 cognitive function. In a study of infants, greater suppression of a heart period based index of
4 vagal tone during the cognitive challenge afforded by the Bayley Scale of Infant
5 Development was associated with more mature cognitive skills and more coordinated motor
6 behaviour (DeGangi et al., 1991). A broadly similar outcome emerged from a more recent
7 study of cardiovascular reactions to a task in which young adults were required to identify a
8 target stimulus among a variety of distractor items (Duschek et al., 2009): R-wave to pulse
9 interval, an index of sympathetic activity, was negatively associated with task performance,
10 whereas respiratory sinus arrhythmia, an index of vagal tone, was positively related to
11 performance. The authors interpret these outcomes as suggesting an association between
12 enhanced sympathetic and reduced vagal cardiovascular influences and improved cognitive-
13 attentional functioning. In contrast, no association between cardiovascular reactivity to
14 memory tasks and task performance has been reported in studies of young (Bucks & Seljos,
15 1994) and older adults (Wright et al., 2005), although in the latter study, superior memory
16 performance was associated with faster heart rate recovery following task exposure. Given
17 the variations in study samples, the physiological parameters measured, and the cognitive
18 tasks employed, it is not surprising that no clear consensus emerges from these studies. With
19 one exception (Wright et al., 2005), all of the studies were small scale and did not adjust for
20 potential confounding variables. More importantly, all of these previous studies measured
21 cognitive ability as performance on the stress reactivity challenge. Stronger tests of the
22 association between cognitive ability and cardiovascular reactivity to mental stress would be
23 afforded by using measures of cognitive ability that are independent of the mental stress task
24 employed to elicit reactivity.

1 In the present study, cardiovascular reactions to acute stress were assessed in a
2 substantial community sample and cognitive ability was then measured five and 12 years
3 later using a standard measure of general intelligence and choice reaction time. Thus,
4 cognitive ability was measured independently of and at different times from mental stress
5 task exposure. We have recently reported from analyses restricted to the oldest of three age
6 cohorts in the West of Scotland study, retrospective associations between reactivity and
7 cognitive ability measured seven years earlier; low heart rate reactivity was characteristic of
8 those with relatively low prior cognitive ability (Ginty et al., 2011). The present analyses are
9 prospective with respect to cognition and data were available for all three age cohorts. Thus,
10 in our previous study we established the possibility of a causal pathway from low cognitive
11 ability to blunted heart rate reactivity. In the present analyses, we test the additional
12 possibility that reactivity predicts cognitive ability in the future, as well as any change in
13 cognitive performance between the two follow-ups. It is also worth noting that choice
14 reaction time has been found to correlate negatively with more traditional measures of
15 general intelligence and indeed has been regarded as a measure of cognitive ability (Rabbitt &
16 Goward, 1994). Based on the balance of previous evidence, including our own recent finding
17 of a retrospective positive association between heart rate reactivity and cognitive ability, as
18 well as research testifying to an association between low or blunted reactivity and a number
19 of adverse health and behavioural outcomes (Carroll et al., 2009a; Carroll et al., in press;
20 Phillips, 2011), it was hypothesised that lower heart rate reactivity would be associated
21 prospectively with relatively lower cognitive ability and slower choice reaction times. Thus,
22 what we are hypothesising is that there might be a bi-directional relationship between
23 cognitive ability and reactivity.

24 **2. Method**

1 2.1. Participants

2 Data were collected as part of the West of Scotland Twenty-07 Study. Participants
3 were from Glasgow and surrounding areas in Scotland, and have been followed up at regular
4 intervals since the baseline survey in 1987 (Ford et al., 1994). The study's principal aim was
5 to investigate the processes that generate and maintain socio-demographic differences in
6 health (Macintyre, 1987). Participants were chosen randomly with probability proportional
7 to the overall population of the same age within a post code area (Ecob, 1987). Thus, this is a
8 clustered random stratified sample. Three narrow age cohorts were chosen (aged 15, 35, and
9 55 years at entry). More complete details of the study are available elsewhere (Carroll et al.,
10 2008; Ford et al., 1994; Phillips et al., 2009).

11 The data reported here are from the third, fourth, and fifth follow-ups. The mean
12 (SD) temporal lag between the third and fourth follow-up visits was 5.5 (1.00) years and
13 between the third and fifth follow-up visits was 12.4 (0.40) years. Cardiovascular stress
14 reactivity was assessed for 1647 participants at the third follow-up. The sample at this time
15 point comprised 592 (36%) 24-year-olds, 624 (38%) 44-year olds, and 431 (26%) 63-year-
16 olds. There were 890 (54%) women and 757 (46%) men, and 772 (47%) were from manual
17 and 870 (53%) from non-manual occupation households. Household occupational status was
18 unavailable for five participants. Overall mean (SD) age at the third follow-up visit was 42.2
19 (15.44) years. The mean (SD) ages of the young, middle-aged, and older age cohorts were
20 24.2 (0.45), 44.56 (0.84), and 63.57 (0.61) years. Cognitive ability, using the Alice Heim-4
21 (AH-4) test and choice reaction time (CRT), was assessed at the fourth and fifth follow-ups.
22 The attrition rate, largely as a result of relocation, between the third and fourth follow-ups
23 was 23%; CRT data were available for 1251 participants at the fourth follow-up. There was
24 little attrition (5%) between the fourth and fifth follow-up and reaction time data were

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1 available for 1189 participants at the fifth follow-up. AH-4 scores were available for 1170
2 and 1148 participants at the fourth and fifth follow-ups respectively. This study was
3 approved by the appropriate Ethics Committees.

4 *2.2. Apparatus and procedure*

5 Participants were interviewed and tested in a quiet room in their homes by trained
6 nurses. During the third follow-up visit household occupational group was classified as
7 manual or non-manual from the occupation of the head of household, using the Registrar
8 General's Classification of Occupations (1980). Head of household was usually the man.
9 Long-standing illness or disability status, hereafter referred to by the latter term, was
10 determined by response to the question, 'Do you have any long-standing illness, disability, or
11 infirmity? By long-standing I mean anything that has troubled you over a period of time or
12 that is likely to affect you over a period of time?' Height and weight were measured and
13 body mass index (BMI) computed. Symptoms of depression were assessed using the
14 Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). The HADS is a
15 well-recognized assessment instrument that comprises 14 items, 7 measuring depression and
16 7 measuring anxiety. The depression subscale emphasises anhedonia and largely excludes
17 somatic items.

18 Participants then undertook an acute psychological stress task, the paced auditory
19 serial addition test (PASAT), which has been shown in numerous studies reliably to perturb
20 the cardiovascular system (Ring et al., 2002; Winzer et al., 1999) and to demonstrate good
21 temporal stability of reactivity (Willemsen et al., 1998). The task comprised a series of single
22 digit numbers presented by audiotape and participants were requested to add sequential
23 number pairs, and at the same time retain the second of the pair in memory for addition to the
24 next number presented, and so on throughout the series. Answers were given orally and, if

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1 The test has been used in other population studies of individuals in the same age range
2 (Singh-Manoux et al., 2005; Rabbitt et al., 2001). At the fourth and fifth follow-ups,
3 participants undertook a CRT task using a portable device originally designed for the UK
4 Health and Lifestyle Survey (Cox et al., 1987). The device consisted of five keys arranged in
5 a shallow arc; the keys were numbered 1, 2, 0, 3, 4. Participants were asked to rest the 2nd
6 and 3rd finger of each hand on the keys labelled 1,2,3,4 and press the corresponding key when
7 one of the four digits appeared above. Participants were given eight practice trials and 40 test
8 trials; the digits 1-4 appeared 10 times during the 40 trials in a random order. The amount of
9 practice given to participants is similar to most studies that relate reaction times to
10 intelligence differences (Deary, 2000). CRT was measured in milliseconds.

11 2.3. *Statistical analysis*

12 Differences in AH-4 scores and CRTs between sexes, household occupational group,
13 and age cohort were explored using analysis of variance (ANOVA). Repeated- measures
14 ANOVAs, using baseline and task values, were undertaken to confirm that the PASAT
15 perturbed cardiovascular activity. Partial eta squared (η^2) is used as a measure of effect size.
16 The relationship between AH-4 scores and CRTs were investigated by Pearson's correlation.
17 Linear regression analyses were used to determine whether cardiovascular reactivity were
18 associated with AH-4 score and CRT five and 12 years later. A series of hierarchical linear
19 regressions were undertaken to determine whether any effects that emerged from the primary
20 analyses withstood adjustment for potential confounding variables. The possible confounders
21 selected were age cohort, sex, household occupational group, disability status, HADS
22 depression, BMI, and baseline cardiovascular levels. All of these have been related to
23 reactivity and/or cognitive ability in this cohort (Carroll et al., 2000, 2007, 2008; Phillips et
24 al., 2011). The main regression analyses were repeated separately for numerical reasoning

1 and verbal reasoning at the two time points testing both unadjusted and fully adjusted models.
2 Finally, regression models were tested that examined the change in cognitive ability over
3 time. In these, AH-4 score and CRT at the fifth follow-up were the dependent variables,
4 cardiovascular reactivity was the independent variable, and we adjusted for earlier AH-4
5 score and CRT at the fourth follow-up in each case. Again, we also tested models that
6 additionally adjusted for all the other covariates.

7 **3. Results**

8 *3.1. Socio-demographics and cognitive ability*

9 The overall mean (SD) AH-4 scores and mean (SD) CRTs at the fourth and fifth
10 follow-ups were 35.28 (11.41) and 35.34 (11.31) respectively and 619.8 (153.31), and 629.5
11 (153.31) milliseconds respectively. The non-manual household group registered higher AH-4
12 scores than the manual occupational group at both follow-ups, $F(1,1164) = 189.25, p < .001,$
13 $\eta^2 = .140, F(1, 1143) = 115.65, p < .001, \eta^2 = .092,$ respectively, as well as faster CRTs, $F(1,$
14 $1245) = 39.26, p < .001, \eta^2 = .031, F(1, 1184) = 15.60, p < .001, \eta^2 = .013,$ respectively.
15 Males displayed significantly higher AH-4 scores at the fourth follow-up than females,
16 $F(1,1169) = 3.95, p = .05, \eta^2 = .003;$ there were no significant difference between genders at
17 the fifth follow-up, nor for CRT at either follow up. The younger cohort registered higher
18 AH-4 scores and faster CRTs than the middle cohort who, in turn, registered higher AH-4
19 scores and shorter CRTs than the oldest cohort at the fourth follow-up, $F(2,1169) = 73.96, p$
20 $< .001, \eta^2 = .112,$ and $F(2,1249) = 398.47, p < .001, \eta^2 = .390,$ respectively, and fifth follow-
21 up, $F(2, 1147) = 122.71, p < .001, \eta^2 = .177,$ and $F(2, 1187) = 354.64, p < .001, \eta^2 = .370,$
22 respectively. Individuals who reported long-standing illness or disability scored substantially
23 lower on the AH4, $F(1,1169) = 22.43, p < .001, \eta^2 = .019,$ and $F(1,1147) = 28.80, p < .001,$
24 $\eta^2 = .025,$ and had markedly slower CRTs, $F(1, 1249) = 45.86, p < .001, \eta^2 = .035, F(1, 1187)$

1 = 41.40, $p < .001$, $\eta^2 = .034$, at the fourth and fifth follow-ups, respectively. The summary
2 statistics are reported in Table 1. AH-4 scores at the two follow-ups were positively
3 correlated, $r(1146) = .87$, $p < .001$, as were CRTs, $r(1030) = .70$, $p < .001$. AH4 scores
4 correlated negatively with CRT at both the fourth, $r(1123) = -.53$, $p < .001$, and fifth, $r(1136)$
5 = $-.55$, $p < .001$, follow-ups.

6 [Insert Table 1 about here]

7 3.2. Cardiovascular reactions to acute stress

8 Two-way (baseline x task) repeated measures ANOVA indicated that on average the
9 PASAT significantly increased cardiovascular activity: for SBP, $F(1,1646) = 1562.32$, p
10 $< .001$, $\eta^2 = .487$, for DBP, $F(1,1646) = 1066.62$, $p < .001$, $\eta^2 = .393$; and for HR, $F(1,1646) =$
11 1132.96 , $p < .001$, $\eta^2 = .408$. The mean baseline and reactivity values are presented in Table
12 3. HR reactivity declined with age, $F(2, 1644) = 21.11$, $p < .001$, $\eta^2 = .408$; with the
13 youngest cohort exhibiting higher reactivity than the middle cohort who, in turn showed
14 higher reactivity than the eldest cohort ($p < .05$ in each case). HR reactivity was also greater
15 in men, $F(1,1645) = 5.23$, $p = .02$, $\eta^2 = .003$, and in participants from non-manual
16 occupational group households, $F(1,1640) = 21.08$, $p < .001$, $\eta^2 = .013$. SBP reactivity varied
17 significantly among the age cohorts, $F(2,1644) = 6.81$, $p < .001$, $\eta^2 = .008$, with the youngest
18 cohort having significantly lower reactivity than the other two cohorts ($p < .05$ in both cases).
19 Women had smaller SBP reactions than men, $F(1,1645) = 16.61$, $p < .001$, $\eta^2 = .010$. DBP
20 reactivity did not vary significantly with age cohort, sex, or household occupational group.
21 The statistics reported above relate to significant group by baseline/task condition
22 interactions. However, for the sake of illustration we report baseline and reactivity in Table
23 2.

24 [Insert Table 2 about here]

1 *3.3 Justification for separate regression analyses for the five and 12 year follow-ups.*

2 In order to justify the separate analyses for the two follow-ups, we tested the time x HR
3 reactivity interaction in a fully adjusted linear mixed model. The interaction was significant
4 for both AH-4 scores, $t(914) = 2.06, p = .04$, and CRT, $t(1005) = 2.40, p = .02$.

5

6 *3.4. Cardiovascular reactivity and future AH-4 performance scores and CRT five years later*

7 In the first model, with no adjustment, HR reactivity was associated with future AH-4
8 performance scores, $\beta = .200, p < .001, \Delta R^2 = .040$; individuals with lower HR reactivity had
9 poorer AH-4 scores five years later. SBP ($p = .33$) and DBP ($p = .95$) reactivity did not
10 significantly predict future AH-4 scores. In regression analyses that adjusted for age cohort,
11 sex, household occupational group, disability status, HADS depression, BMI, and baseline
12 cardiovascular levels, HR reactivity continued to be associated with AH-4 scores, $\beta = .107, p$
13 $= < .001, \Delta R^2 = .010$, with the association in the same direction. The final regression is shown
14 in Table 3. SBP and DBP reactivity did not predict cognitive ability at the fourth follow-up
15 in this fully adjusted model, $p = .25$ and $.67$, respectively. The unadjusted association with
16 HR reactivity are illustrated by plotting AH-4 scores against tertiles of reactivity (Figure 1a).
17 AH-4 scores varied significantly with tertiles of HR reactivity, $F(2,1167) = 27.27, p < .001,$
18 $\eta^2 = .045$. The relationship between SBP and DBP and AH-4 scores were again non-
19 significant. In the unadjusted model, HR reactivity was negatively associated with CRT at
20 the fourth follow-up, $\beta = -.194, p < .001, \Delta R^2 = .038$. SBP ($p = .35$) and DBP ($p = .89$) did
21 not significantly associated with future choice reaction time; individuals with lower
22 HR reactivity had longer CRTs five years later. In the model that adjusted for age cohort, sex,
23 household occupational group, disability status, HADS depression, BMI, and baseline
24 cardiovascular levels, HR reactivity was still negatively associated with CRT, $\beta = -.056, p =$

1 .018, $\Delta R^2 = .003$. The final regression is shown in Table 4. SBP reactivity was also
2 negatively associated with CRT in this fully adjusted model, $\beta = -.055$, $p = .016$, $\Delta R^2 = .003$.
3 DBP reactivity was not associated with future choice reaction time ($p = .78$). The unadjusted
4 association between HR reactivity and CRT are illustrated by plotting CRT scores against
5 tertiles of reactivity (Figure 2a). CRT varied among the tertiles of HR reactivity, $F(2,1284)$
6 $= 27.63$, $p < .001$, $\eta^2 = .042$.

7 3.5. Cardiovascular reactivity and future AH-4 performance scores and CRT 12 years later

8 In the unadjusted model, HR reactivity was associated with AH-4 performance scores
9 at the fifth follow-up, $\beta = .21$, $p < .001$, $\Delta R^2 = .046$; lower HR reactivity was again associated
10 with poorer cognitive ability 12 years later. SBP ($p = .99$) and DBP ($p = .35$) was not
11 significantly associated with future AH-4 scores. In the fully adjusted model, HR reactivity
12 was still positively associated with AH-4 scores, $\beta = .130$, $p < .001$, $\Delta R^2 = .015$. The final
13 regression is shown in Table 3. Neither SBP ($p = .14$) nor DBP ($p = .41$) reactivity were
14 associated with future AH-4 scores in this model. The unadjusted association with HR
15 reactivity is again illustrated by plotting AH-4 scores against tertiles of reactivity (Figure 1b).
16 AH-4 scores varied significantly with tertiles of HR reactivity, $F(2,1145) = 27.73$, $p < .001$,
17 $\eta^2 = .046$. HR reactivity was negatively associated with CRT 12 years later in the unadjusted
18 model, $\beta = -.177$, $p < .001$, $\Delta R^2 = .031$. SBP ($p = .25$) and DBP ($p = .86$) were not. In the
19 fully adjusted model, HR reactivity was still associated with CRT, $\beta = -.078$, $p = .002$, $\Delta R^2 =$
20 $.005$. The associations between SBP ($p = .74$) and DBP ($p = .50$) and future CRT were still
21 not significant. The final regression is shown in Table 4. The unadjusted association
22 between HR reactivity and CRT at the fifth follow-up is illustrated in Figure 2b. CRT varied
23 significantly between the tertiles of HR reactivity, $F(2,1186) = 24.93$, $p < .001$, $\eta^2 = .040$.

24 [Insert Figure 1 and 2 and Tables 3 and 4 about here]

1 *3.6. Cardiac reactivity and future numerical and verbal reasoning ability*

2 In the fully adjusted model, HR reactivity was positively associated with both AH-4
3 numerical and AH-4 verbal reasoning scores at the fourth follow-up, $\beta = .107, p < .001, \Delta R^2$
4 $= .010$, and $\beta = .076, p = .006, \Delta R^2 = .005$, and the fifth follow-up, $\beta = .150, p < .001, \Delta R^2 =$
5 $.020$, and $\beta = .096, p < .001, \Delta R^2 = .008$, respectively.

6 *3.7. Cardiovascular reactivity predicting future change in cognitive ability*

7 In order to examine the association between reactivity and individual differences in
8 change in cognitive ability over time, models were tested with AH-4 score or CRT at the fifth
9 follow-up as the dependent variables and cardiovascular reactivity as the independent
10 variable, with the earlier, fourth follow-up, AH-4 score or CRT, respectively, entered as a
11 covariate. HR reactivity was associated with change in AH-4 score from the fourth to the
12 fifth follow-ups, $\beta = .110, p < .001, \Delta R^2 = .012$. There were no associations for either SBP (p
13 $= .74$) or DBP ($p = .98$). In the model that additionally adjusted for all the other covariates,
14 HR reactivity was still associated with change in AH-4 scores, $\beta = .042, p = .01, \Delta R^2 = .002$.
15 HR reactivity was also associated with CRT at the fifth follow-up after adjusting for CRT at
16 the fourth follow-up, $\beta = -.065, p = .004, \Delta R^2 = .004$. Again, there were no analogous
17 associations for SBP ($p = .51$) and DBP ($p = .72$). The association between HR reactivity and
18 CRT change was still significant in the fully adjusted model, $\beta = -.057, p = .01, \Delta R^2 = .003$.
19 Change in AH-4 score and CRT between the fourth and fifth follow-up was calculated by
20 simple subtraction. Incidentally, the same results as those reported above emerge from fully
21 adjusted regression models for HR reactivity when the dependent variables were the AH-4 (p
22 $= .01$) and CRT ($p = .01$) change scores. To illustrate the HR reactivity associations, change
23 scores for AH-4 and CRT were compared for tertiles of HR reactivity. Whereas change in
24 AH-4 between the two follow-ups was not significant ($p = .35$), change in CRT was, $F(2,$

1 1035) = 6.88, $p = .001$., $\eta^2 = .013$, the highest tertile of HR reactors showed less decline in
2 CRT over time. The summary data are presented in Figure 3a and 3b. Finally, in a
3 supplementary analyses using ANCOVA, we analysed the effect of the interaction between
4 tertiles of HR reactivity and age cohort on change in cognitive ability between the two
5 follow-ups: these analyses were fully adjusted. For CRT, but not AH-4 scores, there was a
6 significant reactivity x cohort interaction, $F(4, 1000) = 2.44$, $p = .04$, $\eta^2 = .010$. This is
7 illustrated in Figure 4 which plots the change in CRT for tertiles of HR reactivity separately
8 for the three age cohorts. As can be seen, the effect of tertiles of reactivity on CRT change is
9 concentrated in the older cohort.

10 [Insert Figure 3 and 4 about here]

11

12 **4. Discussion**

13 This study examined the association between cardiovascular reactivity and future
14 cognitive ability, as indexed by scores on the AH-4 test of verbal and future numerical
15 reasoning and by CRT. Both are accepted measures of cognitive ability (Deary et al., 2001;
16 Rabbit & Goward, 1994). The two measures were strongly, but imperfectly correlated at
17 both follow-ups. Low, not high, HR reactions to acute stress were associated with low AH-4
18 test scores and longer CRTs five and 12 years later. Blood pressure reactivity was not
19 associated with cognitive ability at either time point. Post hoc analyses of tertiles of HR
20 reactivity indicated a dose-response relationship between cardiac reactivity and AH-4 scores
21 and CRT at both follow-ups; blunted HR reactivity was associated with poorer future
22 cognitive ability. HR reactivity was positively associated with both the numerical and verbal
23 reasoning components of the AH-4. These associations between HR reactivity and cognitive
24 ability remained statistically significant in regression models that adjusted for age cohort, sex,

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1 household occupational group, disability status, depressive symptomatology, BMI, and
2 baseline HR.

3 Additionally, HR reactivity was associated with change in cognitive ability over time,
4 i.e., low HR reactivity was associated with poorer AH-4 scores and slower CRTs at the fifth
5 follow-up even after statistical adjustment for cognitive ability at the fourth follow-up, seven
6 years earlier. This suggests that low HR reactivity may be a marker of cognitive aging.
7 Cognitive aging refers to age-related decrements in cognitive function. It would appear that
8 inflammatory markers, such as c-reactive protein (Deary et al., 2009; Weaver et al, 2002;
9 Yaffe et al., 2003) and IL-6 (Deary et al., 2009; Rafnsson et al., 2007; Yaffee et al., 2003),
10 are not only associated with cognitive ability but predict cognitive aging. Increased systemic
11 oxidative stress has also been reported to amplify cognitive aging (Berr et al., 2000; Coyle &
12 Puttafarcken, 2003; Whalley et al., 2004). The present study is the first we know of to find
13 that HR reactivity may also be a predictor of cognitive aging. However, it should be
14 conceded that general intelligence measures are fairly stable over time (Conley, 1984) and,
15 accordingly, may afford less than optimal measures of short term cognitive aging. Further, it
16 has been argued that cognitive aging is mainly accounted for by a decline in inspection time
17 and CRT (Nettelbeck & Rabbitt, 1992). In the present study, the mean AH-4 scores were
18 virtually identical at the two follow-ups, whereas CRT lengthened by 2% between the fourth
19 and fifth follow-ups. Thus, we would expect that if HR reactivity is a marker of cognitive
20 aging, associations would be stronger with CRT as the outcome. Our supplementary analyses
21 were supportive. High HR reactors showed less of a lengthening in CRT over seven years
22 than the rest of the sample; the analogous effect for AH-4 scores was not statistically
23 significant. Finally, the effects of tertiles of reactivity on change in CRT was concentrated in

1 the oldest cohort. This is perhaps hardly surprising, given that it is in this cohort that
2 cognitive aging should be most evident.

3 The observed negative association between cognitive ability and reactivity is in line
4 with that observed in two earlier studies, which found that lower cardiovascular reactivity
5 was associated with poorer performance on the mental stress task (DeGangi et al., 1991;
6 Duschek et al., 2009). However, it should be conceded that two other studies including a
7 sizable study in older adults failed to find an association between reactivity and cognitive
8 ability as revealed by performance on the stress task (Backs & Seljos, 1994; Wright et al.,
9 2005). Nevertheless, the present study is the largest study by some considerable margin to
10 address this issue. In addition, the negative association observed in the present study is
11 consistent with a recent analysis of the oldest cohort in this sample revealing a positive
12 retrospective association between AH-4 scores and HR reactivity seven years later (Ginty et
13 al., 2011). However, this is the first study we know of that links HR reactivity to future
14 cognitive ability. Taken together, our analyses indicate an intimate association between HR
15 reactivity and cognitive ability across the life course. Nevertheless, problems of causation
16 and the direction of causation remain. What the present analyses indicate is that a causal
17 pathway from poor cognitive ability to low reactivity is not the only possibility, but that the
18 link between cognition and reactivity may be bi-directional. Deliberations on causality
19 would have undoubtedly been helped had reactivity been measured at more than one time
20 point and cognitive ability at all time points in the full sample. Unfortunately, as with all the
21 large scale epidemiological studies which measure reactivity, this was not feasible. However,
22 it is worth noting that cardiovascular reactivity has been found to be reasonably stable over
23 time, even across periods of 18 years (Hassellund et al., 2010). Determining causality even
24 in prospective studies is fraught with pitfalls even when a substantial number of variables

1 have been statistically controlled for (Christenfeld et al., 2004). It is possible that some third
2 factor contributes to both cognitive ability and reactivity across the lifecourse. A candidate
3 here may be central motivational dysregulation. By central motivational dysregulation we
4 mean the suboptimal functioning of those systems in the brain, converging at the striatum and
5 ventromedial prefrontal cortex, which appears to shape the motivation of our behaviour.

6 Our results are certainly consistent with the contention that relatively low
7 cardiovascular reactions to acute stress may be a peripheral marker of central motivational
8 dysregulation (Carroll et al., 2009a; Carroll, Phillips et al., in press). The circuits converging
9 in the striatum and the ventromedial prefrontal cortex may be precisely those that support
10 physiological reactivity (Carroll et al., 2009a; Carroll, et al., in press). As cognitive
11 performance requires the integrity of such motivational systems (Busato et al., 2000; Dweck,
12 1986; McClelland et al., 1953; Pintrich & Schunk, 1986), it would be expected that lower
13 rather than higher cardiovascular reactivity would be associated with poorer subsequent
14 cognitive ability, which is precisely what was observed for HR reactivity. Although
15 speculative, it is possible that age-related functional deterioration of central motivational
16 systems, to an extent, underpins the link between HR reactivity and cognitive aging.

17 Our observations are also consistent with a growing body of cross-sectional and
18 prospective evidence that low, not high, cardiovascular reactivity, including HR reactivity, is
19 associated with a range of adverse health and behavioural outcomes, such as obesity (Carroll
20 et al., 2008; de Rooij, et al., in preparation), symptoms of depression (Carroll et al., 2007; de
21 Rooij et al., 2010; Phillips et al., 2011; York et al., 2007), tobacco and alcohol dependence, as
22 well as risk of dependence (al' Absi, 2006; al' Absi et al., 2005; Girdler et al., 1997; Lovallo
23 et al., 2000; Pankin, Dickensheets, Nixon, & Lovallo, 2002; Phillips et al., 2009; Roy et al.,
24 1994), and exercise dependence (Heaney et al., 2011). Thus, it would appear that for health

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1 outcomes such as high blood pressure, hypertension, and atherosclerosis cardiovascular
2 reactivity is a positive predictor, whereas other outcomes are negatively associated with
3 cardiovascular reactivity. This suggests that there might be an inverted U-shaped relationship
4 such that very high and very low reactivity are maladaptive (Carroll et al., 2009a).

5 The present study is not without limitations. First, it should be acknowledged that the
6 observed effect sizes are small. However, our effects are of the same order as the positive
7 associations between cardiovascular reactivity and future resting blood pressure in this
8 sample (Carroll et al., 2003), as well as those observed in other prospective studies of
9 reactivity and subsequent blood pressure status (Carroll et al., 1995; Carroll, et al., 2001;
10 Markovitz et al., 1998; Matthews et al., 1993; Newman et al., 1999) and revealed by a recent
11 meta-analysis (Chida & Steptoe, 2010). Second, given the oral response mode in the
12 PASAT, cardiovascular perturbations could be attributed to speech. However, similar levels
13 of HR reaction to mental arithmetic with and without a speech component have been reported
14 (Sloan et al., 1991) and we have reported substantial cardiovascular reactions to the PASAT
15 when the mode of response was manual rather than oral (Carroll et al., 2009b; Balanos et al.,
16 2010). Third, only blood pressure and HR reactivity were measured. It could have proved
17 instructive to have a more comprehensive assessment of haemodynamics, such as that
18 afforded by impedance cardiography. Further, a continuous rather than an intermittent of
19 blood pressure and HR would have allowed us to chart the time course of acute stress
20 reactivity, allowing us to represent cardiac reactivity as interbeat interval rather than HR.
21 However, the decision to test participants in their own home and the size of the sample
22 precluded more sophisticated measurement. An important distinction is made between
23 cardiac and vascular reactivity in terms of both task and individual specificity (Kamarck et
24 al., 1994). It is important to concede that it was only cardiac reactivity that was consistently

1 linked to AH-4 scores and CRT in the present study. There were no consistent associations
2 between blood pressure reactivity and future cognitive ability. Cardiac reactivity would
3 appear to reflect both β -adrenergic and parasympathetic influences (Balanos et al., 2010;
4 Sloan et al., 1991). Thus, low cardiac reactivity could reflect reduced β -adrenergic drive or
5 less of a reduction in vagal tone during the stress task. Regrettably, in the present study we
6 cannot determine which of these was the predominant mechanism for low cardiac reactivity.
7 However, β -adrenergic blockade has been observed to attenuate cardiac reactivity, but not
8 blood pressure reactivity (Winzer et al., 1999). Thus, reduced β -adrenergic drive would
9 certainly accord with the present pattern of associations. Fourth, the absence of measures of
10 subjective stress and task engagement constitute another limitation, as it means we cannot
11 fully rule out, as an explanation of the current results, the possibility that those with lower
12 cognitive ability tended to disengage from what it is a cognitively challenging stress task.
13 However, it seems to us equally possible that those with lower cognitive ability would have
14 experienced more subjective stress when confronted with a difficult and challenging task.

15 In conclusion, we observed a positive association between HR reactivity and
16 cognitive ability measured five and 12 years later. Reactivity was also associated with the
17 relative change in cognitive ability over time; those with high HR reactivity were less likely
18 to show relative cognitive decline. Our results are consistent with the notion that high
19 cardiovascular stress reactivity may not necessarily be maladaptive and that low or blunted
20 reactivity may also have negative corollaries.

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Table 1. Mean (SD) AH-4 scores and CRT by age cohort, sex, occupational group and disability status at the fourth and fifth follow-ups.

	AH-4 scores				CRT			
	N		Mean (SD)		N		Mean (SD)	
	4th	5th	4th	5th	4th	5th	4th	5th
Age cohort								
Youngest	396	429	38.9 (9.70)	39.8 (9.73)	429	433	538.7 (72.51)	535.0 (63.18)
Middle	478	485	36.2 (11.27)	35.6 (10.84)	496	501	621.1 (86.8)	629.3 (94.9)
Eldest	296	234	29.0 (10.92)	26.7 (10.04)	326	255	724.5 (111.5)	790.2 (210.40)
Sex								
Male	529	530	36.0 (11.37)	35.7 (11.11)	574	541	616.2 (110.49)	626.0 (163.85)
Female	641	618	34.7 (11.41)	35.0 (11.48)	677	648	622.8 (118.00)	632.4 (143.97)
Occupational group								
Manual	507	495	30.4 (11.10)	31.44 (10.95)	562	525	642.0 (124.20)	648.9 (178.22)
Non-manual	658	649	39.1 (10.17)	38.4 (10.63)	684	660	601.7 (102.93)	613.8 (128.21)
Disability status								
No disability	1136	1119	35.6 (11.32)	35.6 (11.22)	1212	1156	615.9 (110.77)	624.7 (148.68)

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Disability	34	29	26.2 (10.63)	24.3 (9.43)	39	33	740.0 (160.62)	796.0 (213.54)
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Table 2. Mean (SD) values of SBP, DBP, and HR baseline and reactivity by age cohort, sex, and occupational status.

	SBP		DBP		HR	
	Baseline	Reactivity	Baseline	Reactivity	Baseline	Reactivity
Age cohort						
Yongest (n = 592)	120.0 (15.07)	10.1 (10.24)	73.4 (10.08)	6.8 (9.04)	67.5 (11.00)	10.0 (10.56)
Middle (n = 624)	127.1 (18.08)	12.3 (11.44)	80.6 (11.13)	7.1 (8.03)	66.7 (11.17)	7.7 (10.00)
Eldest (n = 431)	144.4 (21.68)	12.3 (13.92)	83.8 (11.17)	7.0 (8.92)	65.7 (9.92)	6.1 (7.74)
Sex						
Male (n = 757)	134.7 (18.25)	12.8 (11.77)	81.2 (11.18)	7.2 (8.43)	64.7 (10.43)	8.7 (9.73)
Female (n = 890)	124.3 (21.07)	10.4 (11.70)	76.8 (11.56)	6.8 (8.81)	68.4 (10.84)	7.6 (9.83)
Occupational group						
Manual (n = 722)	130.5 (21.44)	11.1 (12.22)	79.3 (11.93)	6.5 (9.07)	67.0 (11.26)	6.9 (9.53)

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Non-manual (n =872)	127.8 (19.58)	11.8 (11.39)	78.4 (11.29)	7.3 (8.24)	66.5 (10.40)	9.1 (9.90)
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Table 3. Predictors of AH-4 score at the fourth and fifth follow-up in the fully adjusted heart rate reactivity regression model.

	AH-4 scores 4 th follow-up			AH-4 scores 5 th follow-up		
	β	<i>p</i>	ΔR^2	β	<i>p</i>	ΔR^2
Age cohort	-.263	<.001		-.361	<.001	
Sex	-.051	.050		-.031	.226	
Occupational group	-.352	<.001		-.282	<.001	
Disability status	-.061	.019		-.084	.001	
HADS depression	-.083	.001		-.122	<.001	
BMI	-.021	.438		-.006	.804	
Baseline heart rate	-.006	.814	.254	.013	.621	.284
Heart rate reactivity	.107	<.001	.010	.130	<.001	.015

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Table 4. Predictors of CRT at the fourth and fifth follow-up in the fully adjusted heart rate reactivity regression model.

	CRT 4 th follow-up			CRT 5 th follow-up		
	β	<i>p</i>	ΔR^2	β	<i>p</i>	ΔR^2
Age cohort	.584	<.001		.561	<.001	
Sex	.021	.336		.026	.271	
Occupational group	.124	<.001		.084	<.001	
Disability status	.077	.001		.083	<.001	
HADS depression	.135	<.001		.104	<.001	
BMI	-.010	.656		-.012	.600	
Baseline heart rate	.019	.422	.438	-.045	.064	.389
Heart rate reactivity	-.056	.018	.003	-.078	.002	.005

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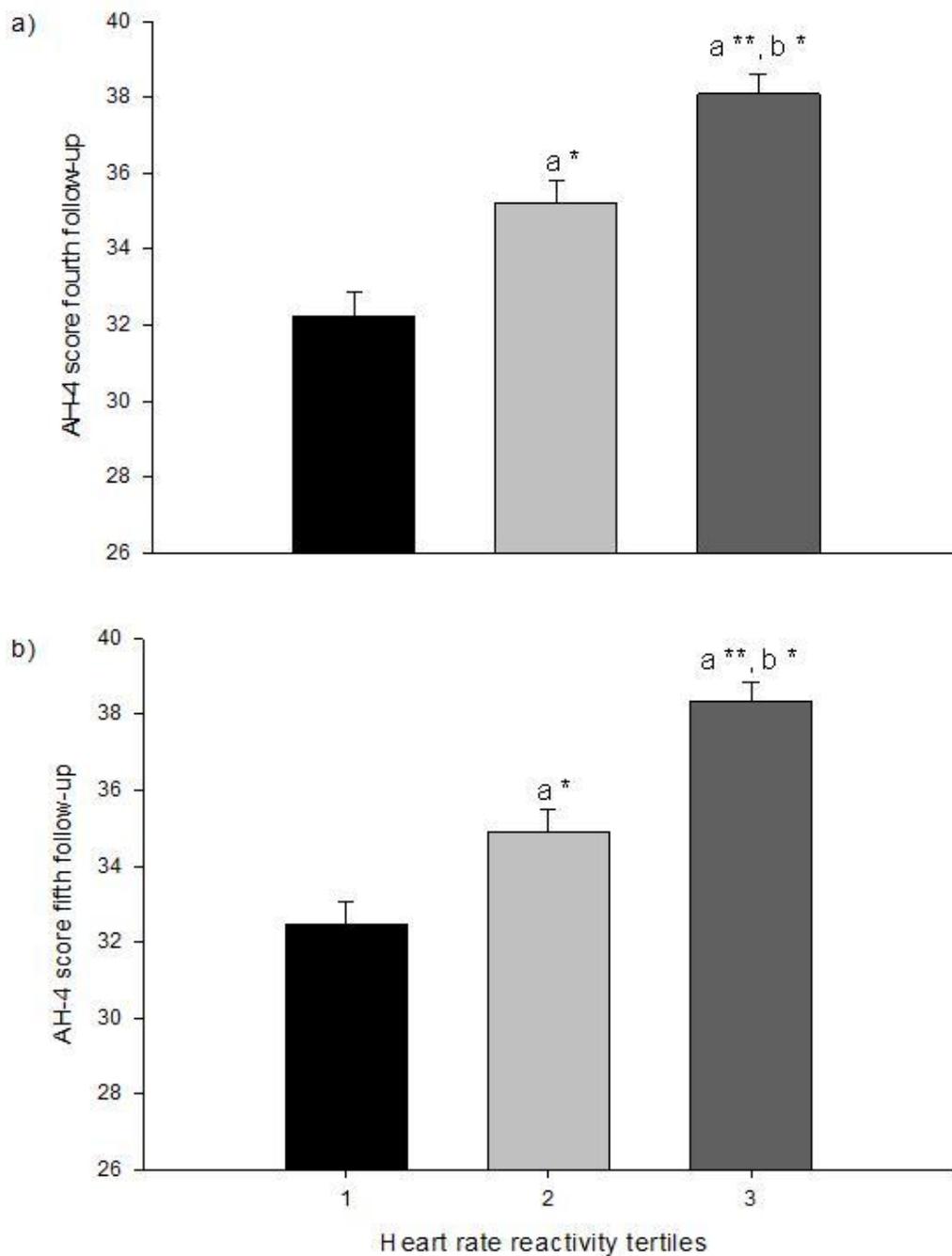
Figure Captions

Figure 1. a) AH-4 scores at the fourth follow-up by tertiles of heart rate reactivity, b) AH-4 scores at the fifth follow-up by tertiles of heart rate reactivity

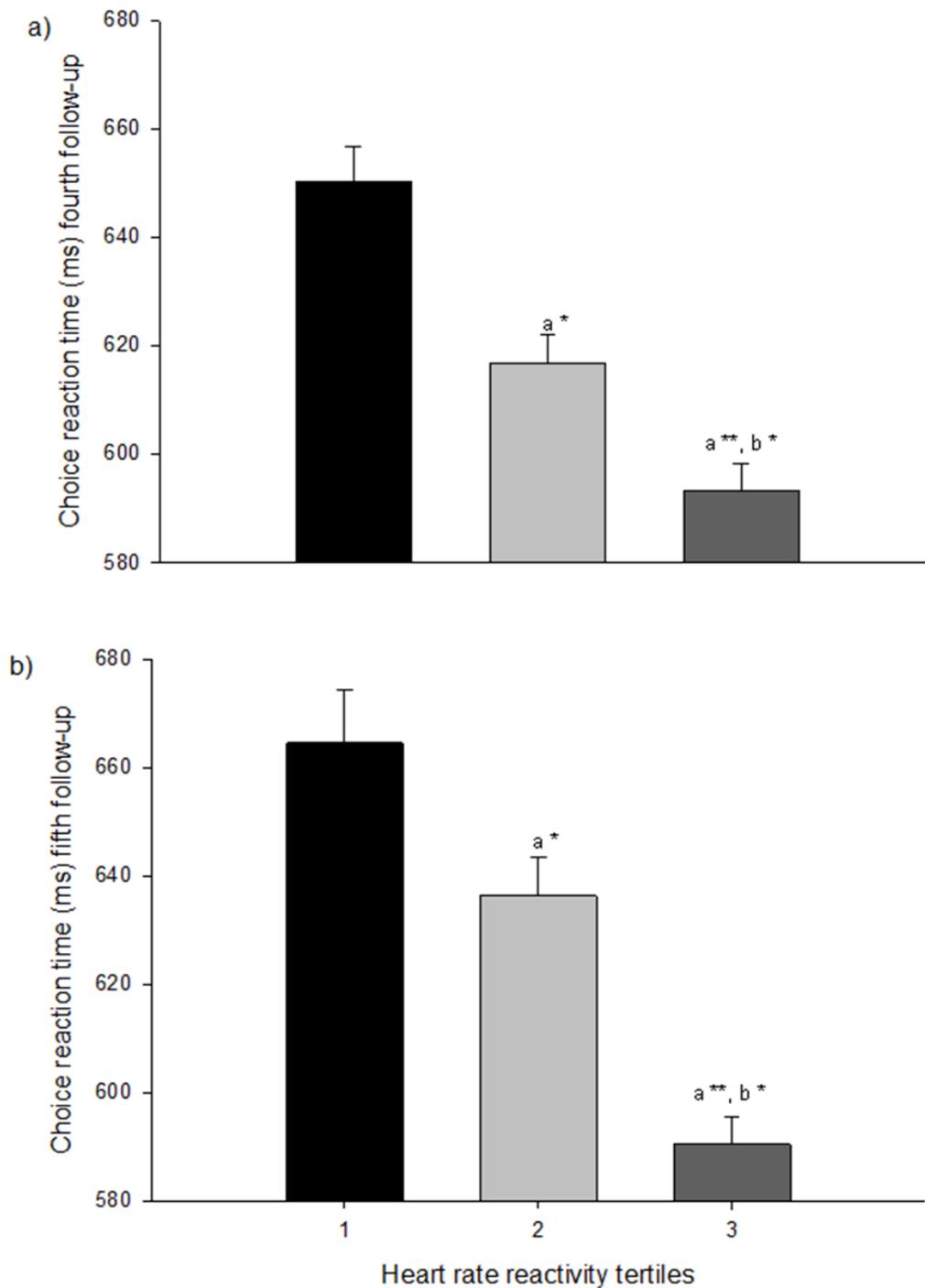
Figure 2. a) CRTs at the fourth follow-up by tertiles of heart rate reactivity, b) CRTs at the fifth follow-up by tertiles of heart rate reactivity

Figure 3. a) CRT change between fourth and fifth follow-up by tertiles of heart rate reactivity, b) AH-4 change score between fourth and fifth follow-up by tertiles of heart rate reactivity

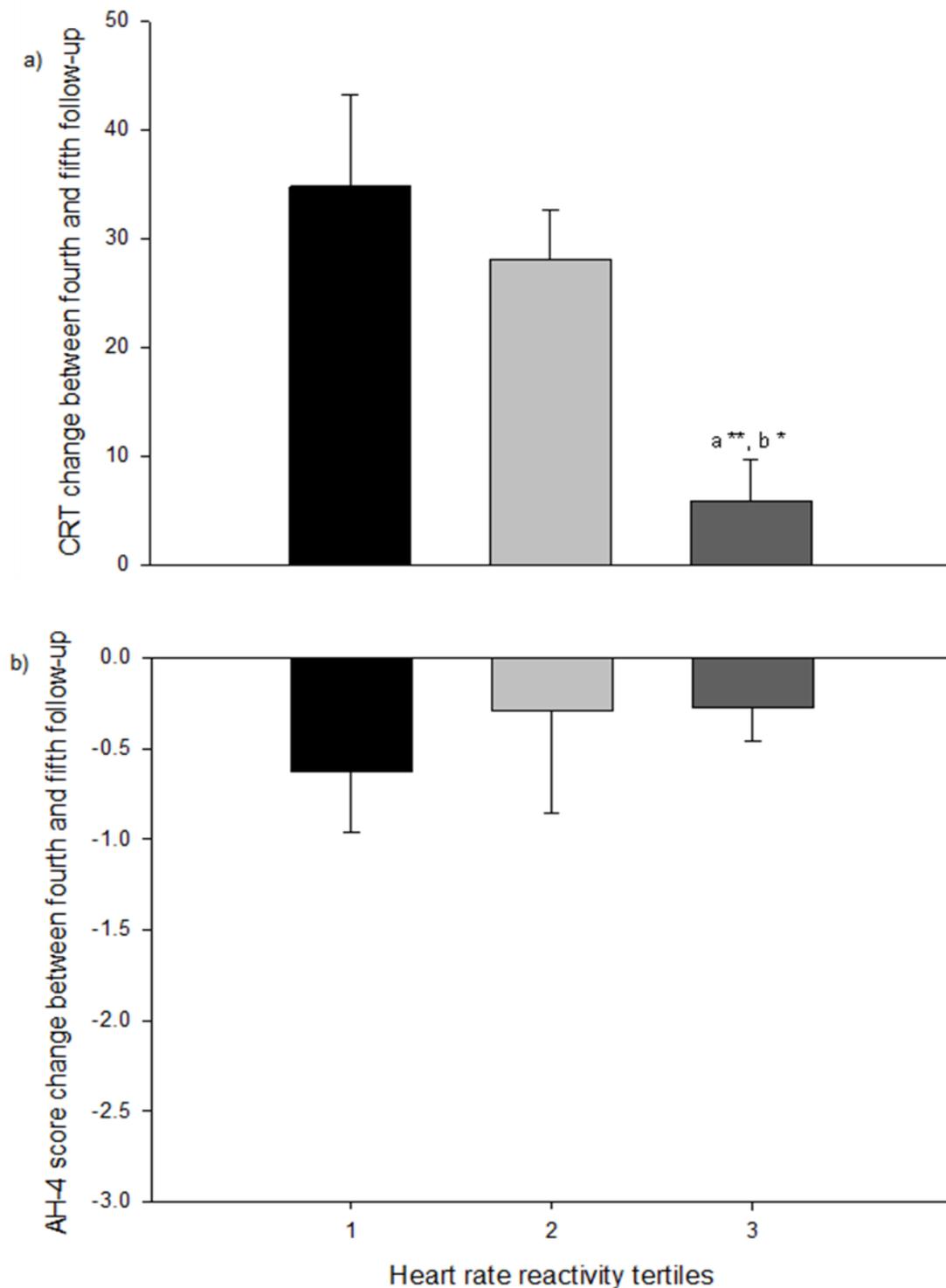
Figure 4. CRT change between fourth and fifth follow-up for tertiles of HR reactivity separately for the three age cohorts



Note: a = significantly different from 1st, b = significantly different from 2nd.
* = $p < .01$, ** = $p < .001$



Note: a = significantly different from 1st, b = significantly different from 2nd.
* = $p < .01$, ** = $p < .001$



Note: a = significantly different from 1st, b = significantly different from 2nd.
* = $p < .05$, ** = $p < .001$

