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The association between razor clam consumption and memory in the CoASTAL cohort

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ABSTRACT

This study represents a preliminary effort to examine the potential impacts of chronic, low level domoic acid (DA) exposure on memory in the CoASTAL cohort over the first four years of data collection (Wave 1). Five hundred and thirteen adult men and women representing three Native American Tribes were studied annually with standard measures of cognition and razor clam consumption (a known vector of DA exposure) over a four-year period. In addition, a pilot metric of DA concentration exposure was used which took into consideration average DA concentration levels in source beaches, as well as the amount consumed. Based upon generalized estimating equations (GEE) analysis, controlling for age, sex, race, year, education level, tribe, and employment status, findings indicated that high razor clam consumers (15 or more per month) had isolated decrements on some measures of memory ($p = 0.02–0.03$), with other cognitive functions unaffected. The relatively lower memory scores were still within normal limits, and were thus not clinically significant. The pilot DA exposure metric had no association with any other aspect of cognition or behavior. There is a possible association between long-term, low-level exposure to DA through heavy razor clam consumption and memory functioning.

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1. Introduction

The potential impact of domoic acid (DA) exposure to human health was discovered in 1987 in Montreal, Canada (Perl et al., 1990a,b; Teitelbaum, 1990; Teitelbaum et al., 1990). Many people who consumed affected mussels harvested from the Prince Edward Island (PEI) region suffered serious medical illnesses requiring hospitalization. Their symptoms included vomiting, abdominal cramps, diarrhea, headache, amnesia, seizures, coma and in some cases, death. Because of the memory problems observed in the majority of cases presented for medical treatment, comprehensive neuropsychological testing was performed on 14 survivors four months to one year after exposure and illness onset. Of the 14 people studied, one case had a completely normal neuropsychological profile and another had a generalized intellectual impairment which was so severe, it precluded reliable testing. The remaining 12 cases had varying degrees of memory loss and, in several well-publicized cases, a true amnesia was discovered within the context of otherwise intact cognitive abilities (Zatorre, 1990). Postmortem studies identified abnormalities in the hippocampus and related structures, including the dorsal medial thalamus, amygdala, nucleus accumbens, insula and sub-frontal cortex—all of which are associated with the memory system of the brain (Teitelbaum et al., 1990; Zola-Morgan and Squire, 1993). The remarkable memory disorder in many of the patients, combined with the postmortem results, led to use of the term "amnesic shellfish poisoning" (ASP) to describe the syndrome associated

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with DA neurotoxicity. However, numerous questions remain regarding those individuals with only gastrointestinal symptoms, younger people who did not seek medical treatment or did not have premorbid medical problems, and people with the least symptoms during the PEI outbreak (Teitelbaum, 1990; Teitelbaum et al., 1990).

Domoic acid was reported for the first time in the US in the late summer of 1991 when pelicans and cormorants were poisoned in Monterey Bay, California after feeding on anchovies contaminated with DA (Walz et al., 1994). Within the next few years, DA was detected in shellfish, including Dungeness crabs and razor clams, on the coasts of Washington and Oregon, (Wekell et al., 1994). After extensive studies, razor clams became known as the most significant vector for DA exposure in humans. This is because razor clams retain the toxin for up to one year in the natural environment, or several years after being processed, canned or frozen (Wekell et al., 1994). Because of aggressive monitoring in the state of Washington by the Washington State Department of Health, DA levels for high-risk beaches are well-documented. Accordingly, over the past decade, persistent low levels of DA in razor clams appeared to be the norm with concentrations rarely exceeding the regulatory guidance level of 20 ppm on select beaches. When DA levels approached 20 ppm, beaches were closed for harvesting razor clams which has been protective, with only 24 probable and 1 confirmed case of ASP reported in humans in 1991 (Trainer and Hardy, 2015).

Meanwhile, coastal residents, including Native American subsistence harvesters, as well as recreational harvesters, continue to enjoy razor clams, which may contain low levels of DA. Since DA is a known neurotoxin, the question is raised as to whether or not chronic low level exposure may have some impact on human health. Animal studies, including those of rodents and non-human primates, reported changes in behavior and hippocampal cell death following exposure to both high and low levels of DA (Scallet et al., 1993; Sobotka et al., 1996; Slikker et al., 1998; Doucette et al., 2004; Schwartz et al., 2014). These animal models alerted us to the possibility that people who consistently consume shellfish with low levels of DA may be at risk for some level of mild neurotoxicity. Since there is no biological test or established method to determine the amount of DA people have consumed in razor clams in the past 20 years, one can only rely on estimates from consumption surveys and harvest data. These estimates, at minimum, need to be based upon consumption risk (how many razor clams did the individual consume) and general source data from shellfish samples at relevant harvesting beaches (did they collect and eat razor clams from a beach with documented low levels of DA that week or month). This study was initiated to determine whether or not a plausible relationship may exist between long-term, low-level DA exposure via razor clam consumption and human health problems. The goals of the study were twofold: (1) to examine high-, low-, and non-razor clam consumers with respect to performance on memory tasks and (2) to determine the utility of a gross metric of possible DA exposure, i.e., the product of consumption (the average number of razor clams consumed per month that year) over time (the annual mean measured domoic concentration, in parts per million, in razor clams at the beaches from which the participant harvested clams).

2. Methods and materials

2.1. Participants

Participants included 513 adult men and women from the CoASTAL cohort (Wave 1) ages 18 years and older. The CoASTAL cohort represents a random sample of Native Americans from three Pacific NW tribes who, by virtue of their access to razor clam beaches and traditional diets, regularly consume razor clams (Fialkowski et al., 2010). The Wave 1 participants represent a cohort that was annually studied over a four year time period. Further details about recruitment methods and baseline data may be found in Tracy et al. (2016).

2.2. Measures

2.2.1. Demographic information

General demographic, developmental, academic, social, occupational, medical, neurologic, drug use, psychiatric, and exposure history were assessed using a modified version of the Boston Occupational and Environmental Neurological Health Questionnaire (Feldman, 1999). In light of the large amounts of fish and other seafood consumed by the CoASTAL cohort, this investigative team directly examined the possibility of methylmercury exposure. Based upon these studies, there were no elevated levels of methylmercury in this cohort that could potentially confound the cognitive findings (Tracy et al., 2016).

2.2.2. Cognitive assessment

Cognitive functions were assessed with standardized neuropsychological measures designed to evaluate memory within the context of other cognitive domains. The categories of cognitive functions assessed were: *simple and complex attention and concentration* [Wechsler Adult Intelligence Scale-III (WAIS-III) Digit Span (Wechsler, 1997); WAIS-III Digit Symbol Coding (Wechsler, 1997); Trail Making Test, Parts A and B (Reitan, 1992)], *constructional praxis* [WAIS-III Block Design (Wechsler, 1997)], *verbal memory* [California Verbal Learning Test-II Standard and short form (CVLT-II), (Delis et al., 2000)], *psychomotor speed and dexterity* [Lafayette Grooved Pegboard (Lafayette Instrument Company, 2002)], and *cognitive flexibility* [Trail Making Test, Part B (Reitan, 1992)]. Psychological functioning was assessed using standard measures of depression and anxiety including the Beck Depression Inventory-II (BDI-II; Beck et al., 1996) and the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983), respectively. Higher scores on each of these measures indicate more severe symptoms of depression and anxiety.

2.2.3. DA exposure

Razor clam consumption (as a potential marker for risk of DA exposure) was measured using the Shellfish Assessment Survey. This measure was previously validated by this research team for use in this regional, Native American population (Fialkowski et al., 2010). Participants were divided into non-consumer, high-consumer and low-consumer groups based upon the overall distribution of consumption scores. Individuals consuming 15 or more razor clams/month were considered high consumers and people who ate less were low consumers. Potential exposure to DA was also measured as the product of consumption (the average number of razor clams consumed per month that year) over time (the annual mean measured domoic concentration, in parts per million, in razor clams at the beaches from which the participant harvested clams).

2.3. Procedures

Written informed consent was obtained from all participants in compliance with standard procedures required by the University of Maryland Institutional Review Board. All measures were administered annually for four years by trained examiners in private field offices in the participants' communities. Exclusionary

Table 1
Characteristics of adult and geriatric participants, by razor clam consumer group, Year 1.

	Sample composite	Consumer group[a]			
		None	Low	High	*p* value[b]
Study participants, % (*n*)		20% (101)	53% (270)	28% (142)	
Age, mean ± SD	36.3 ± 12.4	32.2 ± 11.5	37.1 ± 12.9	37.6 ± 11.3	<0.01[c]
% Female, (*n*)	59% (300)	69% (69)	57%(153)	55% (78)	0.07
Married, %, (*n*)	31% (151)	26% (25)	34% (86)	29% (40)	0.36
Employed, % (*n*)	51% (258)	52% (52)	50%(131)	53% (75)	0.80
Educational level, % (*n*)					0.26
<High school (<12 year)	16% (59)	16% (13)	13% (25)	20% (21)	
High school (12year)	41% (157)	48% (39)	42% (82)	35% (36)	
13 or more years of school completed	43% (163)	37% (30)	45% (86)	45% (47)	

[a] Consumer groups include None: No razor clams consumption that year, Low: Consumed fewer than 15 razor clams per month, High: Consumed at least 15 razor clams per month. Razor clam consumption groups were averaged and combined over fall/winter and spring/summer periods.
[b] *p* values from Pearson's *chi*-square test, except one-way ANOVA.
[c] One-way ANOVA.

criteria included a history of severe dementia, severe head injury, or other psychiatric or neurological disorder which precluded understanding informed consent or assessment procedures. The background assessments, cognitive, and shellfish consumption procedures took about 2.5 h per annual visit, for which participants were reimbursed $50 upon the completion of each visit.

2.3.1. Data analysis

Data were reviewed for completeness and distribution. Responses for the fall/winter and spring/summer seasons within each year were averaged for each participant to produce their consumer category each year. In Year 1, the cut-off of 15 razor clams per month placed roughly twice as many participants into the low consumer group as into the high consumer group.

Bivariate analysis at Year 1 revealed differences in baseline characteristics between the no-, low-, and high- consumer groups, using one-way analysis of variance and Pearson's *chi*-square tests. Data for all time points were considered in the analysis that sought associations between razor clam consumption and resulting scores on cognitive performance tests; this analysis used generalized estimating equations (GEE) to compare mean scores for each test between the three consumer groups,

Table 2
Cognitive data for performance on neuropsychological screening battery, by razor clam consumer group (*n* = 513 participants with 1502 observations).

	All groups	Consumer group[a]				
		None	Low		High	
	mean ± SD	mean ± SD	mean ± SD	*p* value[b]	mean ± SD	*p* value
WAIS-III digit symbol coding, *n* observations	1499	484	691		324	
T score	46.8 ± 9.4	47.2 ± 9.6	47.3 ± 9.5	0.41	45.1 ± 8.8	0.03
Age-corrected	9.1 ± 2.8	9.2 ± 2.9	9.2 ± 2.9	0.42	8.6 ± 2.6	0.05
WAIS-III block design, *n*	1490	479	689		322	
T score	48.2 ± 8.9	48.7 ± 9.3	48.5 ± 9.0	0.88	46.9 ± 8.3	0.17
Age-corrected	9.5 ± 2.7	9.7 ± 2.8	9.6 ± 2.7	0.90	9.1 ± 2.5	0.22
WAIS-III digit span, *n*	1494	480	690		324	
T score	45.6 ± 7.2	46.0 ± 7.6	45.6 ± 7.1	0.68	44.9 ± 6.7	0.73
Age-corrected	8.7 ± 2.2	8.9 ± 2.3	8.7 ± 2.1	0.83	8.6 ± 2.0	0.98
CVLT trial 5 free recall, *n*	1494	484	689		321	
T score	41.0 ± 10.8	42.4 ± 11.1	40.5 ± 10.6	0.36	40.0 ± 10.4	0.03
CVLT short delay free recall, *n*	1491	484	686		321	
T score	43.8 ± 10.7	45.4 ± 11.0	43.4 ± 10.6	0.51	42.1 ± 10.2	0.02
CVLT long delay free recall, *n*	1492	483	687		322	
T score	43.0 ± 11.4	44.5 ± 11.9	42.7 ± 11.0	0.74	41.7 ± 10.9	0.17
Trailmaking test: part A, *n*	1502	484	694		324	
T score	50.0 ± 10.1	49.5 ± 10.3	50.2 ± 10.4	0.81	50.2 ± 9.3	0.89
Trailmaking test: part B, n	1438	471	658		309	
T score	49.1 ± 9.5	49.5 ± 10.1	48.9 ± 9.4	0.34	49.3 ± 8.5	0.85
Laf. grooved pegboard, dom. hand, n	1476	482	678		316	
T score	41.0 ± 11.2	42.0 ± 11.1	41.1 ± 11.3	0.56	39.2 ± 10.8	0.14
Laf. Grooved pegboard, non-dom. hand, *n*	1460	478	671		311	
T Score	41.5 ± 10.3	41.9 ± 9.8	41.6 ± 10.8	0.99	40.6 ± 9.8	0.66
Beck depression inventory-II, *n*	1494	483	688		323	
Raw score	10.1 ± 9.5	10.6 ± 9.9	9.9 ± 9.3	0.13	9.7 ± 9.2	0.27
State trait anxiety inventory, *n*	1494	482	688		324	
State: age-corrected	50.4 ± 10.2	49.7 ± 10.3	50.5 ± 10.1	0.90	51.2 ± 10.4	0.97
Trait: age-corrected	52.4 ± 11.5	52.0 ± 11.7	52.5 ± 11.2	0.88	52.5 ± 12.0	0.99

[a] Consumer groups include None: No razor clams consumption that year, Low: Consumed fewer than 15 razor clams per month, High: Consumed at least 15 razor clams per month. Razor clam consumption groups were averaged and combined over fall/winter and spring/summer periods.
[b] Generalized estimating equations for differences in score, comparing low or high consumer group to the non-consumer group, accounting for repeated measures and year. Models represented in this table are not adjusted for other covariates.

accounting for repeated measures within subject. Multivariable GEE models sought the same relationships, but were adjusted for year of data collection, age, sex, race (Native American or not), tribe, education level, and employment status. All GEE models were fit to a Gaussian distribution family and used the identity link function. A final series of GEE models evaluated the associations between DA exposure and scores on cognitive performance tests. All coefficients for these GEE models were multiplied by 1000. Relationships were considered statistically significant at $p \leq 0.05$. All data analysis was performed using STATA 12 (StataCorp, 2007).

3. Results

The sample included 513 adult participants who had sufficient data in Year 1 to be categorized into a consumer group (Table 1). The average age of the sample was 36.3 years old (standard deviation 12.4 years). More than half of the participants were low consumers in Year 1, and fewer than half were high consumers. One in five participants did not consume razor clams in Year 1. The majority of the sample was female and unmarried. Approximately half of the sample reported current employment. Non-consumers of razor clams tended to be younger than low- and high-consumers.

Accounting for repeated measures but before adjustment for other covariates, consumption of razor clams showed few significant relationships with scores on cognitive performance tests (Table 2). High consumers had significantly lower *T* scores ($p = 0.03$) and age-corrected scores ($p = 0.05$) on the WAIS-III Digit Symbol subtest (a timed task of sustained attention/concentration, clerical speed, and accuracy). High consumers also had lower scores two memory subtests: CVLT Trial 5 Free Recall ($p = 0.03$) and CVLT Short Delay Free Recall ($p = 0.02$) tests than did the non-consumers. The relationships between razor clam consumption and scores on the Beck Depression Inventory or the State-Trait Anxiety Inventory were not statistically significant in these models.

Adjusting for age, sex, race, year, education level, and employment status, high consumption of razor clams remained a significant predictor of lower scores on two of the CVLT memory recall tests (Table 3). Participants in the high exposure group, on average, scored 1.67 points lower on the CVLT Trial 5 Free Recall than did non-consumers ($p = 0.04$) and 1.40 points lower on the CVLT Short Delay Free Recall ($p = 0.05$). Consumption was negatively correlated with scores on the Beck Depression Inventory in these multivariable models, with low consumers scoring 1.10 points lower ($p = 0.04$) and high consumers scoring 1.32 points lower ($p = 0.05$) on average than non-consumers. When mean DA levels at specific beaches were included as the exposure variable, DA toxin exposure did not significantly predict any of the cognitive outcomes.

4. Discussion

This is the first cohort study to assess whether chronic, low-level exposure to DA via razor clam consumption has a potential

Table 3
Adjusted associations between seafood consumption and performance on neuropsychological screening battery ($n = 513$ participants with 1502 observations).

	Consumer group					Avg. razor clam DA exposure	
	None	Low		High			
	Coeff.	Coeff.	*p* value[a]	Coeff.	*p* value[a]	Coeff.[b]	*p* value[a]
WAIS-III digit symbol coding							
Age-corrected	Ref.	−0.10	0.46	−0.29	0.08	−0.47	0.27
WAIS-III block design							
Age-corrected	Ref.	+0.07	0.61	−0.21	0.22	−0.47	0.30
WAIS-III digit span							
Age-corrected	Ref.	−0.05	0.67	−0.11	0.49	−0.13	0.74
CVLT Trial 5 free recall							
T score	Ref.	−0.57	0.38	−1.67	0.04	−2.28	0.28
CVLT short delay free recall							
T score	Ref.	−0.50	0.38	−1.40	0.05	−1.56	0.41
CVLT long delay free recall							
T score	Ref.	−0.10	0.87	−0.65	0.41	−2.61	0.20
Trailmaking test: part A							
T score	Ref.	+0.09	0.89	−0.18	0.82	−1.15	0.59
Trailmaking test: part B							
T score	Ref.	−0.45	0.44	+0.24	0.75	+1.65	0.39
Laf. grooved pegboard, dom. hand							
T score	Ref.	+0.05	0.94	−1.13	0.18	−3.96	0.08
Laf. grooved pegboard, non-dom. hand							
T Score	Ref.	+0.20	0.75	−0.21	0.79	−0.11	0.96
Beck depression inventory-II							
Raw score	Ref.	−1.10	0.04	−1.32	0.05	−1.48	0.41
State trait anxiety inventory							
State: age-corrected	Ref.	−0.75	0.26	−0.99	0.23	−1.70	0.44
Trait: age-corrected	Ref.	−0.80	0.24	−1.39	0.10	−3.30	0.14

Adjusted for age, sex, race (Native American or not), year, education level, and employment status.
Razor clam consumption groups were averaged over fall/winter and spring/summer:
- None: Did not consume razor clams that year.
- Low: Consumed fewer than 15 razor clams per month.
- High: Consumed at least 15 razor clams per month.

Razor clam domoic acid exposure: calculated as: (average number of razor clams consumed per month) time (average concentration, in parts per million, of domoic acid in razor clams at the beach(es) from which the participant ate clams that year).

[a] Generalized estimating equations, accounting for repeated measures.
[b] Coefficients for "number of razor clams consumed per month" are multiplied by 1000.

impact on human health. In this preliminary study, well-validated measures of cognition and dietary consumption were employed to assess memory and razor clam consumption as an important first step toward identifying exposure risk (Tracy et al., 2016). Findings suggest that very high razor clam consumers (greater than 15 clams per month) performed worse on memory measures than a reference group of non-consumers or low consumers. These findings could not be otherwise explained by explained by age, sex, race, educational level, or employment status. The isolated memory decrements, within the context of otherwise stable cognition in other domains, is consistent with the cognitive pattern of DA exposure in the index PEI exposure cases, although in attenuated form (Zatorre, 1990).

The pilot DA toxin exposure measure that was used, e.g., average DA measurements from specific beaches multiplied by the number of clams consumed over the previous four years, did not predict any of the cognitive outcomes. Therefore, it is possible that the memory decrements in high consumers reflected DA exposures that pre-dated the start of this study, when DA levels were significantly higher. Alternatively, the DA concentration exposure measure may have lacked sensitivity to exposure. That is, this measure assumed that DA levels at the source beaches were constant in all razor clams in time and space. This generally is not the case as there can be considerable variability in DA concentrations among razor clams collected at the same time, from the same beach (Wekell et al., 2002). Moreover, DA levels can quickly and unpredictably fluctuate over time, once again making it difficult to accurately determine DA concentrations in a given consumed razor clam. Alternatively, it is possible that despite controlling for all known potential confounds, DA exposure level was not related to the memory findings. The final arbiter of this interpretation will be more advanced methods of assessing and modeling DA exposure.

An important question is the extent to which differences in memory performance among razor clam consumers has any clinical or practical significance. Despite the fact that the high consumer group had lower memory scores, the group as a whole still performed within normal limits on the memory measures. Further studies are underway to determine the functional impact of possible DA related memory inefficiencies in this cohort and to examine subgroups within the high consumers. Meanwhile, the high consumers will continue to be followed closely over time as part of the larger CoASTAL cohort study. Finally, in the interest of protecting human health, after consultation with tribe leaders, participant communities have been advised to consider consuming fewer than 15 razor clams per month.

This study of the CoASTAL cohort highlights the importance of monitoring the cognitive functions of people at risk of DA poisoning. Additional studies are underway using alternate exposure metrics, collecting accurate "real-time" data on sourcing and consuming clams through cell phone technology (see Boushey et al., 2016), and focusing on children and geriatric subgroups of the CoASTAL cohort. Future research is needed to facilitate the development of a reliable exposure metric for at risk individuals. This includes the development of advanced technologies for assessing dietary exposure as well as the identification of biomarkers for DA exposure in humans. With this knowledge, the complex interaction between the consumption of razor clams with low levels of DA and cognitive decline could be clarified.

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