

The Effect of Emotion on Visual Attention to Information and Decision Making in the Context of Informed Consent Process for Clinical Trials

REBECCA A. FERRER^{1*}, JENNIFER TEHAN STANLEY², KAITLIN GRAFF¹, WILLIAM M. P. KLEIN¹, NINA GOODMAN¹, WENDY L. NELSON¹ and SILVIA SALAZAR¹

¹National Cancer Institute, Rockville, MD, USA

²University of Akron, Akron, OH, USA

ABSTRACT

The aim of this study was to examine the influence of emotion on visual information processing and decision making in the context of informed consent. Researchers are ethically obligated to ensure informed consent in clinical trials; however, many volunteers have unrealistic expectations about the value of an experimental therapy. Moreover, suboptimal participation rates for clinical trials may be partially attributable to perceptions that ethical obligations to volunteers are not met. This study examines whether discrete negative emotions (fear, anger, and sadness) differentially influence information processing, visual attention, and decisions in the context of clinical trial informed consent. Community participants completed a standard emotion induction (or control) and then read an actual consent form from a clinical trial while eye movements were tracked. Fear and anger produced the most prominently different patterns of systematic processing and visual attention, such that fear induced longer fixations to information presented, whereas anger induced shorter fixations. Moreover, among women only, fear increased decisions to participate, compared with anger and neutral emotion. Examinations of associations between eye-tracking variables and self-reported outcomes indicated that for angry participants only, less systematic processing was associated with greater decisions to participate. Negative emotions of any kind decreased accurate perceptions of trial benefit. These patterns suggest a complex interplay among emotion, processing style, and decision making. Future research is necessary to further probe these effects among potential clinical trial volunteers. Published 2016. This article is a U.S Government work and is in the public domain in the USA.

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KEY WORDS emotion; visual attention; information processing; informed consent

Clinical trials are essential for developing effective methods to prevent and treat disease. Despite the necessity to increase participation (Collyar, 2000; Cox & McGarry, 2003), researchers have an ethical obligation to ensure that participants enroll voluntarily and with full understanding (Faden & Beauchamp, 1986). Thus, informed consent for clinical trials should provide all information relevant to making a meaningful decision about whether or not to participate (Brody, McCullough, & Sharp, 2005). However, volunteers in clinical trials often hold mistaken beliefs about the trial, have unrealistic expectations about an experimental treatment's medical value, believe they will receive the treatment most likely to benefit them, or expect they are more likely to benefit than other volunteers (Appelbaum, Lidz, & Grisso, 2004; Bergamin, Johansson, & Wilking, 2011; Bergenmar, Molin, Wilking, & Brandberg, 2008; Daugherty et al., 1995; Jansen et al., 2011). Moreover, suboptimal participation rates for clinical trials (Collyar, 2000) may be partially attributable to perceptions of inadequate trial information provision (Mills et al., 2006). Thus, one potential avenue to increase patient understanding and voluntary clinical trial enrollment is to improve the informed consent process.

Long and complex informed consent documents are one barrier to understanding and decision making. Although informed consent is intended to involve a discussion between

the researcher and potential volunteer, the consent document is the primary vehicle for conveying information (Jefford & Moore, 2008). Indeed, investigators rarely assess volunteers' understanding (Brown, Butow, Ellis, Boyle, & Tattersall, 2004; Jenkins, Fallowfield, Souhami, & Satwell, 1999), and volunteers believe they are informed about a trial even when objectively they are not (Bergamin et al., 2011; Bergenmar et al., 2008). Thus, it is critical to facilitate systematic reading and understanding of consent documents among potential trial volunteers. Efforts to improve informed consent have had variable success, and the only methods to modestly but reliably improve the process are intensive and potentially resource prohibitive (i.e., extensive person-to-person interaction; Flory & Emanuel, 2004). By identifying conditions under which informed consent is compromised, researchers can better know when such intensive efforts to improve informed consent are warranted. However, other than broad categories like mental illness, education, and age (Flory & Emanuel, 2004), factors associated with better or worse understanding of clinical trials in informed consent settings have received scant attention.

Emotion may be one such factor that is particularly influential in information processing and decisions in the context of informed consent for clinical trials (Ferrer et al., in press). A growing literature continues to demonstrate the robust influence of discrete emotions on judgments and decision making, including information processing (Angie, Connelly, Waples, & Kligyte, 2011; Han, Lerner, & Keltner, 2007). In particular, evidence suggests the tendency to rely on

*Correspondence to: Rebecca A. Ferrer, Basic Biobehavioral and Psychological Sciences Branch, National Cancer Institute, Rockville, MD 20892 USA. E-mail: ferrerra@mail.nih.gov

systematic or heuristic information processing (Chaiken & Eagly, 1989) can be influenced by emotions (Lerner & Tiedens, 2006; Tiedens & Linton, 2001). Importantly, research has demonstrated that the influence of emotion via appraisals and action tendencies can linger after the emotional experience has ceased (Andrade & Ariely, 2009). Moreover, discrete negative emotions can differentially influence visual attention, even if they are of the same valence (Ford et al., 2010). Thus, examining whether selective visual attention is influenced by discrete emotions in the context of clinical trial informed consent is a necessary research pursuit.

Although emotion is a relevant factor in all clinical trial decision making, it is likely to be particularly important in the context of clinical trials for life-threatening diseases such as cancer, given that they evoke a host of negative emotions (Barracough, 1999; Stanton, Danoff-burg, & Huggins, 2002; Stanton & Snider, 1993). Clinical trials themselves are also emotion-laden, where hope for efficacy or fear of side effects or ineffectiveness can hover over participation decisions (Daugherty et al., 1995; Jansen et al., 2011; Penman et al., 1984; Rodenhuis et al., 1984). Thus, it is imperative to conduct basic research to understand how emotion functions to influence information processing and decision making in the clinical trial informed consent process. In turn, clinical trial informed consent is a health decision making domain that provides an excellent context for understanding the role of visual attention in emotion-driven information processing and risk perception effects. No study to date has investigated the direct influence of emotion and visual processing on understanding and decision making among potential clinical trial volunteers.

This experimental study examines how emotions influence systematic reading and recall of the informed consent document, decisions to participate, and satisfaction with consent during the informed consent process for a simulated cancer prevention clinical trial. We chose anger, fear, and sadness because these emotions are prevalent in cancer contexts (Barracough, 1999) and may differentially influence systematic processing and decision making (Han, Lerner, & Keltner, 2007). For example, anger has been shown to trigger heuristic information processing and risk-seeking, whereas fear triggers more systematic processing and risk aversion (Lerner & Keltner, 2001; Lerner & Tiedens, 2006; Parker & Isbell, 2010; Weary & Jacobsen, 1997).

We employed a simulated informed consent paradigm to increase experimental control, consistent with formative research on informed consent decision making across the literature (Davis, Berkel, & Holcombe, 1998; Flory & Emanuel, 2004). We assessed systematic reading patterns using eye tracking to record how participants visually engaged with the information in the informed consent, where longer fixation durations and longer overall reading time are indicative of systematic reading (Kuo, Hsu, & Day, 2009; Rayner, 1998; Velichkovsky, 1999; Velichkovsky, Rothert, Kopf, Dornhöfer, & Joos, 2002).¹

¹Although attention can move without eye movement (Posner et al., 1980), the converse is not true (Hoffman & Subramaniam, 1995; Just & Carpenter, 1980).

We expected the most prominent effects when comparing fear with anger, given that anger has been shown to result in heuristic information processing and action tendencies toward approaching risk, whereas fear results in systematic processing and risk avoidance (Carver & Harmon-Jones, 2009; Han et al., 2007; Frijda, 1986; Lerner & Tiedens, 2006). We also anticipated that sadness would differ from the neutral condition, given that sadness can increase systematic processing but involves action tendencies to seek reward that can result in risk-seeking behavior (Bodenhausen et al., 1994; Frijda, 1986; Lerner et al., 2004).

Hypothesis 1: We predicted that fear and anger would have sharply contrasting effects on information processing and visual attention, such that anger would be associated with more heuristic processing and fear with more systematic processing, relative to each other and the control group. We predicted that sadness would also result in more systematic information processing, compared with neutral. Hypothesis 2: We predicted that anger would result in less understanding of the clinical trial, compared with fear and neutral, whereas fear would result in better understanding of the trial, compared with anger and neutral. We also predicted that sadness would result in greater understanding compared with anger and neutral. Hypothesis 3: We predicted that anger would increase decisions to participate in the trial, compared with fear and neutral conditions. However, although sadness was expected to result in patterns of processing and understanding similar to those exhibited in the fear condition, we predicted that sadness would result in increased decisions to participate in the trial (due to reward-seeking tendencies).

We also conducted exploratory analyses to examine whether sex moderates the effects of emotion. Women are underrepresented in clinical trials (Ford et al., 2006; Jagsi et al., 2009; Murthy, Krumholz, & Gross, 2004), and low female enrollment in clinical trials has been attributed to perceptions of higher risk for harm (Ding, Powe, Manson, Sherber, & Braunstein, 2007), demonstrating a need to understand whether contextual factors differentially influence women's understanding of the trial and decisions to enroll. We anticipated there may be some sex differences in the effects of negative emotions, given differences observed in previous research. For example, anger (Fessler, Pillsworth, & Flamson, 2004) and stress (Lighthall, Mather, & Gorlick, 2009; Mather & Lighthall, 2012) both increase risk-taking among men but not women. Finally, we conducted exploratory analyses to examine whether the associations among eye-tracking outcomes and self-reported outcomes differed by condition.

METHODS

Participants

Recruitment was conducted by a contractor and involved posting advertisements about the study to local billboards and craigslist.org. Of the 352 individuals who responded, 214 participated and received \$50 remuneration (the remainder were ineligible, were no longer interested in participating when called to schedule, or did not show up to the

experiment). Individuals were ineligible if they had (i) conditions that interfere with eye tracking (e.g., permanently dilated pupils, cataracts, and glaucoma), (ii) cancer (as the informed consent form was for a cancer prevention trial), or (iii) previously participated in a clinical trial. Ten participants were excluded from analyses (five guessed the study hypothesis, four had cancer and were erroneously enrolled, and one timed-out of the study), yielding a sample of 204 participants (age $M = 43.33$ years; $SD = 15.35$ years; range = 19–80 years; women = 136). Ninety-nine participants were Caucasian (48.5%), 77 were African American (37.7%), 10 were Asian (4.9%), 2 were American Indian (1%), and 16 (7.8%) classified themselves as another race. Thirteen participants were Hispanic or Latino (6.4%). Eighteen (8.8%) participants had poor eye-tracking calibration, and 12 (5.8%) had insufficient eye-tracking data. These participants were excluded in accordance with previous studies (Isaacowitz, Toner, Goren, & Wilson, 2008; Mogg, Bradley, Field, & De Houwer, 2003) yielding a sample of 174 participants for eye-tracking analyses. One participant with an extremely high outlier value ($>4 SD$ above the mean) was identified; this contributed to high skew and kurtosis of outcome measures and was removed from analyses to effectively normalize the distribution.

Procedure

Procedures for this study were approved by a National Cancer Institute Institutional Review Board. Participants were informed they would take part in two separate studies (Lench, Flores, & Bench, 2011)—a study on “perspective-taking” and a study on “pre-testing an informed consent document”—because the effects of emotion on decision making can be attenuated or eliminated when participants are aware of the potential that emotion may be influential (Han et al., 2007). First, participants were randomly assigned to watch one of the four previously validated film clips (ranging 2.5–4 minutes; Rottenberg, Ray, & Gross, 2007) to induce sadness (a scene from *The Champ* (Zeffirelli, 1979) showing a young boy crying over his father’s death), anger (a scene from *My Bodyguard* (Bill, 1980) where a young man, surrounded by onlookers, is bullied), fear (a scene from *Silence of the Lambs* (Demme, 1991) where a female FBI agent chases after a suspect in a dark basement), or no emotion (a clip from the nature documentary *Alaska’s Wild Denali* (Hardesty, 1997) showing scenes of the wilderness). They then completed a computer-based questionnaire to evaluate the effectiveness of the induction.

Next, participants moved to a second computer, containing a Tobii Studio TX300 eye-tracking device equipped with infrared iris reading sensory optics and remote camera that allows eye tracking while participants are seated naturally. The eye-tracking equipment has a sampling rate of 300 Hz. Participants were seated such that their faces were approximately 65 cm away from the 23-inch monitor. Participants’ eyes were calibrated (9 calibration points) to the tracker. Participants’ gaze was tracked and time-locked as they read through a real 18-page consent form for a completed cancer prevention clinical trial, titled “Pilot Study on the Bioactivity of Vitamin D in the Skin after Oral Supplementation,” which

was presented such that each page took up the entirety of the screen. Fixations were defined as 60 ms or more, consistent with Tobii default settings (selected based on a Tobii Studios review of extant literature; Kliegl et al., 2004; Radach, Huestegge, & Reilly, 2008; Salojärvi et al., 2005; see <http://www.tobii.com/en/eye-tracking-research/global/library/white-papers/the-tobii-i-vt-fixation-filter/>). They then completed another computer questionnaire. Participants were debriefed about the purpose of the study, including about the separate studies cover story.

Self-report measures

Emotions were assessed with a modified version of the Positive Affect Negative Affect Scale, which asks participants to rate their current emotions on a scale of 1 (not at all) to 7 (extremely) (Watson, Clark, & Tellegen, 1988). Three previously validated (e.g., Lerner & Keltner, 2001; Lerner et al., 2003) pertinent emotion scales were anger (hostile, angry, and irritable; $\alpha = .88$), fear (scared, nervous, and afraid; $\alpha = .92$), and sadness (sad, upset, and distressed; $\alpha = .79$).

Perception of trial benefit was assessed with two items: “Participants may receive no benefit from participating in this study” (43% correct) and “Participants may choose whether to take vitamin D while enrolled in the study” (50% correct). The decision to participate in the trial was assessed with two items ($r = .72$): “If I was at high risk for skin cancer, I would participate in this trial” (1 = “strongly disagree” to 7 = “strongly agree”) and “This trial seems like a good option for those at high risk for skin cancer” (1 = “strongly disagree” to 7 = “strongly agree”). Satisfaction was assessed with a single item (Arora et al., 2011): “In general, how satisfied are you with the information provided in the consent form about the clinical trial?” (1 = “very dissatisfied” to 5 = “very satisfied”).²

Eye-tracking measures

Average fixation duration was calculated by dividing the total fixation duration for the entire consent form by the total number of fixations; this was considered a measure of systematic reading, given that longer fixation durations have been previously shown to demonstrate more systematic reading (Just & Carpenter, 1980; Kuo et al., 2009; Rayner & Fischer, 1996). We also examined total reading time as a secondary assessment of systematic reading. Moreover, each page of the consent form contained designated areas of interest (AOIs); these were used to calculate fixation duration to specific portions of the consent form: *procedural details* and *benefit information* (see online supplementary materials for detailed information about specific AOIs that contribute to each variable). For both of these portions of the consent form, we controlled for individual differences in overall fixation duration by calculating a ratio using the participants’

²Recall of side effects presented, risk perceptions about side effects, and visual attention to side effects-related information was also assessed. However, because recall was high and the trial involved mostly very minor side effects, these outcomes were treated as ancillary and are presented in the online supplementary materials.

average fixation duration to the entire consent form (following Li, Fung, & Isaacowitz, 2011).³

Analyses

We conducted a series of independent general linear models and planned comparisons of main effects and interactions, using SAS 9.2 (SAS Institute Inc., Cary NC, USA). The primary eye-tracking outcomes were as follows: (i) average fixation duration; (ii) fixation to procedural details; (iii) fixation to trial benefit information; and (iv) overall time spent reading. The primary self-reported dependent variables were as follows: (i) accurate perception of benefit; (ii) hypothetical decisions to participate; and (iii) satisfaction with the consent. Specifically, we conducted a separate set of analyses of covariance (ANCOVAs) for each eye-tracking and self-reported outcome. We included age as a covariate because our age range was wide (19–80 years) and older age is associated with slower processing speed, longer reading times, and greater fixation durations (Rayner, Reichle, Stroud, Williams, & Pollatsek, 2006; Salthouse, 1996). For each outcome, first, we examined main effects of emotion condition. Then, in a second ANCOVA, we examined whether emotion interacted with sex to predict a particular outcome. When a significant emotion condition by sex interaction emerged, we conducted analyses stratified by sex to probe the nature of the interaction.

We also examined whether eye-tracking variables were associated with self-reported outcomes and whether the strength of this association was influenced by experimental condition. We were specifically interested in whether attention to procedural details and benefits information in the consent form was associated with knowledge about the study (accurate perceptions about trial benefits) and hypothetical decisions to participate. Because the study was not powered to examine moderated mediation, we regressed the eye-tracking variables on each self-reported outcome. All eye-tracking variables were entered in each outcome regression simultaneously, and non-significant eye-tracking predictors were removed from final reported models, with one exception: because the average fixation duration was incorporated into the ratios for fixation to specific details in the consent form (see preceding text; Li, Fung, & Isaacowitz, 2011), separate regressions were undertaken with average fixation duration as a predictor to avoid violating statistical assumptions of predictor independence.

RESULTS

Induction checks

Inductions were found to be effective based on planned comparisons comparing participants in each emotion condition to (i) neutral condition participants and (ii) all other participants combined, with target emotion as the outcome: Anger-neutral, $F(1, 210)=67.32$, $p<.0001$, $d=1.12$; Anger-all, $F(1, 210)=45.73$, $p<.0001$, $d=.92$; Fear-neutral,

$F(1, 210)=33.91$, $p<.0001$, $d=.80$; Fear-all, $F(1, 210)=8.00$, $p=.0051$, $d=.39$; Sadness-neutral, $F(1, 210)=111.05$, $p<.0001$, $d=1.44$; Sadness-all, $F(1, 210)=31.90$, $p<.0001$, $d=.77$. These effect sizes are consistent in magnitude with those observed in previous studies (Lench et al., 2011). Moreover, the reduced effect sizes when examining comparisons involving the target emotion versus all other groups are consistent with findings that some degree of “contamination” when inducing negative emotions is common (e.g., inducing anger may also to some degree induce fear; Gross & Levenson, 1995). However, given that these comparisons were still statistically significant, the emotion inductions were deemed successful.

Hypothesis 1: Information processing. Table 1 contains ANCOVA and planned comparison results. Those in the fear condition ($M=.304$, $SD=.047$) engaged in more systematic processing (longer average fixation duration), than those in the anger condition ($M=.284$, $SD=.050$), a difference that was significant in planned comparisons, ($F=3.89$, $p=.050$; Figure 1). Similarly, those in the fear condition spent more time fixating to details about the benefits of participation ($M=.128$, $SD=.030$) than did those in the anger condition ($M=.113$, $SD=.025$), a significant difference ($F=5.71$, $p=.018$).

Interestingly, those in the fear and anger conditions spent significantly more time fixating to procedural details than those in the neutral condition ($F=5.37$, $p=.022$; $F=7.80$, $p=.006$, respectively). A visual inspection of the data suggested the possibility that participants in the sadness condition spent less time fixating to study details than participants in other conditions; however, post hoc Tukey tests indicated that participants in the sadness condition paid less attention to study details than those in the anger condition ($Mdiff=-.022$, $p=.030$) but not to those in the fear ($Mdiff=-.019$, $p=.073$) or neutral conditions ($Mdiff=-.012$, $p=.421$).

Hypothesis 2: Understanding and satisfaction with consent. Table 1 contains ANCOVA and planned comparison results. Accurate benefit perceptions were decreased by anger ($p=.002$), sadness ($p=.005$), and fear ($p=.033$). There were no main effects of emotion on satisfaction with the consent form. However, there was a significant sex by emotion interaction, such that fearful men were more likely to report satisfaction ($p=.046$). Anger also resulted in an increase in satisfaction among men ($p=.042$).

Hypothesis 3: Participation decisions and satisfaction. Table 1 contains ANCOVA and planned comparison results. A significant sex by emotion condition interaction emerged (Figure 1), such that among women, fear resulted in a significant reduction in decisions to participate compared with both neutral ($p=.036$) and anger conditions ($p=.038$).

Associations between eye-tracking outcomes and self-reported outcomes

Fixation to study details was associated with accurate perceptions of study benefits only in the sadness condition

³A fixation count variable was calculated for each of these four sections; the pattern of and significance of results were entirely consistent with duration ratio, and as such, these analyses are omitted but are available upon request.

Table 1. Analyses of covariance and planned comparisons

	Main effects full sample <i>n</i> = 174			Emotion by sex interaction <i>n</i> = 174			Female <i>n</i> = 115			Male <i>n</i> = 60		
	<i>F</i>	<i>p</i>	<i>d</i>	<i>F</i>	<i>p</i>	<i>d</i>	<i>F</i>	<i>p</i>	<i>d</i>	<i>F</i>	<i>p</i>	<i>d</i>
Average fixation duration												
Age (years)	.57	.452	.11									
Emotion	1.37	.255	.18	.80	.494	.14						
Anger versus neutral	.76	.383	-.13	.61	.437	-.11						
Sadness versus neutral	.16	.687	-.06	.03	.862	.03						
Fear versus neutral	1.16	.283	.16	.60	.438	.11						
Anger versus fear	3.89	.050	-.30	2.34	.128	-.23						
Fixation to procedural details												
Age (years)	2.08	.151	.22									
Emotion	2.97	.033	.26	.23	.877	.07						
Anger versus neutral	7.80	.006	-.42	.01	.908	-.02						
Sadness versus neutral	2.58	.110	-.24	.02	.897	.02						
Fear versus neutral	5.37	.022	-.35	.41	.521	.10						
Anger versus fear	.19	.660	-.07	.25	.614	-.08						
Fixation to benefit information												
Age (years)	.35	.557	.09									
Emotion	2.15	.096	.22	.22	.882	.07						
Anger versus neutral	.66	.418	-.12	.17	.680	-.06						
Sadness versus neutral	.15	.703	-.06	.12	.730	.05						
Fear versus neutral	2.58	.110	.24	.06	.809	.04						
Anger versus fear	5.71	.018	-.36	.03	.854	-.02						
Reading time												
Age (years)	4.88	.029	.33	4.99	.027	.42	4.99	.028	.42	.03	.864	.05
Emotion	1.01	.392	.15	1.26	.292	.21	1.26	.292	.21	2.30	.087	.39
Anger versus neutral	2.89	.091	-.26	.97	.328							
Sadness versus neutral	.27	.606	-.08	.14	.708							
Fear versus neutral	.42	.517	-.09	7.13	.008	.18	.98	.323	.18	5.81	.019	-.62
Anger versus fear	1.04	.309	-.15	3.14	.079	.27	3.62	.060	-.35	.74	.393	.22
Accurate benefit perceptions												
Age (years)	.06	.804	.03									
Emotion	3.98	.009	.28	1.71	.166	.18						
Anger versus neutral	9.75	.002	-.44	.93	.336	.13						
Sadness versus neutral	8.09	.005	-.40	1.64	.202	.18						
Fear versus neutral	4.61	.033	-.31	.04	.839	.03						
Anger versus fear	.96	.328	-.13	1.45	.229	.17						
Hypothetical participation decisions												
Age (years)	2.30	.131	-.21				1.19	.277	-.19	1.55	.218	-.31
Emotion	1.23	.300	.16	2.12	.100	.20	2.35	.075	.27	1.05	.377	.26
Anger versus neutral	.01	.910	-.01	.04	.832	.03						
Sadness versus neutral	2.77	.098	-.23	.21	.644	.06						
Fear versus neutral	.95	.330	-.14	4.13	.043	.28	4.48	.036	-.37	1.27	.264	.28
Anger versus fear	.76	.385	-.12	4.87	.028	.31	4.38	.038	.36	1.49	.226	-.30
Satisfaction with consent												
Age (years)	1.75	.187	-.19				3.57	.061	-.33	1.47	.230	-.31
Emotion	.91	.437	.13	2.63	.053	.23						
Anger versus neutral	2.01	.158	.20	2.09	.080	.20	.06	.809	.04	4.29	.042	.52
Sadness versus neutral	.11	.739	-.04	2.62	.107	.23						
Fear versus neutral	<.01	.996	-.01	7.73	.006	.39	2.26	.135	-.26	4.16	.046	.51
Anger versus fear	2.03	.156	-.20	.78	.379	-.12						

Bold indicates significance of *p* < .05.

($\beta = .331, p = .035$). Average fixation duration was significantly and positively associated with accuracy concerning study benefits only among neutral condition participants ($\beta = .297, p = .045$). This association was not observed in the remainder of the sample ($\beta = .038, p = .668$). In the anger condition, average fixation duration was significantly and negatively associated with decisions to participate ($\beta = -.325, p = .027$). This association was not observed in the remainder of the sample ($\beta = -.054, p = .541$).

DISCUSSION

By comparing systematic reading effects for sadness, anger, and fear, this research provides important evidence regarding the influence of discrete emotions on information processing and related visual attention patterns when reading a clinical trial informed consent document, as well as hypothetical decisions to participate in the trial. Differences in visual attention and decision making were most pronounced between

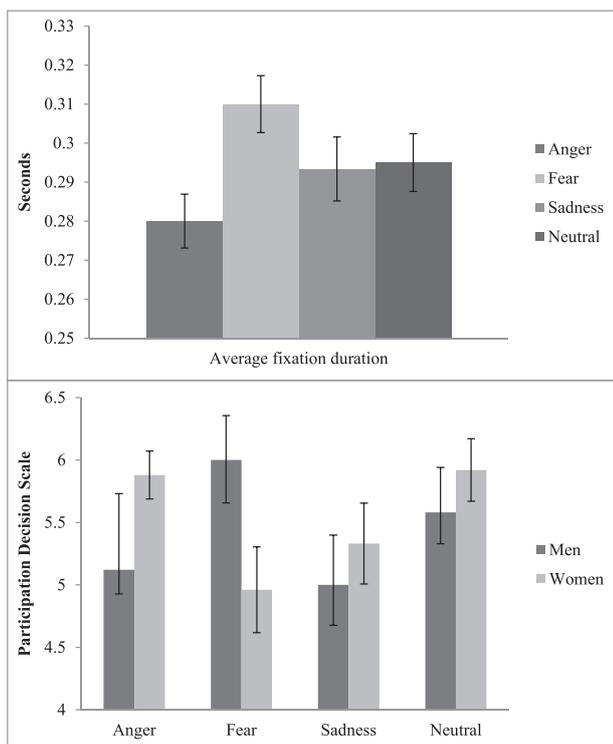


Figure 1. Top panel: average fixation duration by condition; Bottom panel: participation decisions by condition and sex

the fear and anger conditions. Specifically, those in the fear condition engaged in overall more systematic processing, compared with those in the anger condition, consistent with predictions (Han et al., 2007; Lerner & Keltner, 2000; 2001). This finding was consistent examining both overall depth of processing (average fixation duration) and fixation duration to details about the benefits of participation. Interestingly, however (and inconsistent with predictions), both fear and anger condition participants had significantly longer duration time for procedural details (compared with both sadness and neutral condition participants).

Findings on self-reported measures were somewhat consistent with predictions: among women, anger increased and fear decreased decisions to participate. However, no such differences were observed among men. Sadness did not influence decisions to participate, possibly because such decisions may be seen as approach decisions but not necessarily contextualized as rewards to seek. Additional research is necessary to examine whether sadness increases decisions to participate in clinical trials when such decisions are seen as reward-seeking (e.g., if a participant actually had cancer and viewed participation as a potentially curative action). Inconsistent with predictions, accurate benefit perceptions (a measure of comprehension and recall) were uniformly low among all negative emotion condition participants, and both fear and anger increased attention to procedural details, suggesting that some study effects are consistent with valence rather than discrete emotion explanations. Of note, men in the fear condition were more satisfied with the consent process than men in the other conditions.

A pattern of associations between eye-tracking and self-reported outcomes also emerged. Specifically, and importantly,

all negative emotions may have disrupted normal processing of information about the trial benefits, given that only sad participants exhibited the expected association between systematic processing and accurate perceptions about trial benefits. Additionally, fixation to study details was related to accurate perception of study benefits only in the sadness condition; thus, although sadness did not trigger systematic processing consistently with other studies (e.g., Bodenhausen et al., 1994), these results suggest the possibility that sad individuals may be primed to benefit from systematic information processing when it occurs.

In the anger condition, fixation to study details was *negatively* associated with decisions to participate (i.e., among angry participants who read more systematically, decisions to participate were lower.) Notably, this means that angry participants who read the consent form less systematically—a tendency actually exacerbated by anger—were *more* likely to participate. Future research is necessary to further probe the mechanisms underlying this effect; however, it is possible that angry individuals are primed to better process information heuristically (Moons & Mackie, 2007) and were thus better equipped to make a decision about participation.

This experiment contributes to a growing body of evidence suggesting that same-valenced (here, negative) emotions may influence judgments and decisions very differently. Although in some instances negative emotions performed similarly, more often nuanced and different effects were observed for specific negative emotions. Quite consistently, anger and fear contrasted most starkly in their effects, such that anger decreased and fear increased, systematic processing. This effect was observed both for average fixation duration and fixation to study details. Moreover, fearful women were least likely to express willingness to participate, and fearful men were most likely to be satisfied with the consent process. Finally, associations among eye-tracking variables and decisions to participate were different between the fear and anger conditions and, although correlational, were consistent with the hypothesis that fear and anger have different risk-related action tendencies.

Further, this experiment generates a hypothesized factor (i.e., emotion) that could explain why clinical trial participation rates are low and thus can inform interventions to ethically increase enrollment in clinical trials. Our results demonstrate that fear may be a powerful deterrent to clinical trial participation among women, although this finding is tempered because participants were not actual potential clinical trial volunteers. This is an important hypothesis to examine in future research because, overall, women respond to negative events with stronger fear reactions than men (Grossman & Wood, 1993; Lerner, Gonzalez, Small, & Fischhoff, 2003), and naturally occurring fear in response to disease diagnosis or a clinical trial itself may be one potential reason for observed underrepresentation of women in clinical trials (Ford et al., 2006; Jagsi et al., 2009; Murthy et al., 2004). Thus, it is possible that psychosocial interventions designed to reduce anxiety among cancer patients (Fors et al., 2011; Ross, Boesen, Dalton, & Johansen, 2002) may have the unintended benefit of generating more openness to participation in clinical trials.

This study has several limitations. First, the study involves a simulated rather than actual clinical trial. Although this allows for greater experimental control and is common practice in informed consent research (Davis et al., 1998; Flory & Emanuel, 2004), it is possible that these results may not generalize to actual potential clinical trial volunteers, particularly among clinical populations. Future research should examine how emotion influences understanding and decision making among actual potential clinical trial participants, including healthy volunteers and clinical populations. Moreover, informed consent for clinical trials is a dynamic process that involves more than a consent form. Although the informed consent document is important (Brown et al., 2004; Jefford & Moore, 2008; Jenkins et al., 1999) and limiting interaction increases experimental control, future research should examine emotion in the context of a dynamic consent setting. We did not assess whether participants were familiar with the film clips, or participants' emotional state prior to the emotion induction, raising the possibility that pre-existing emotion or past experience may confound inductions. This risk is attenuated by randomization, making it unlikely that any one condition would be overweighted by individuals with any particular levels of pre-existing emotions or past experience. Moreover, induction checks indicated the films had the intended effects (although induction checks were limited by the fact that only the modified Positive Affect Negative Affect Scale was used to validate emotion inductions). Finally, the analyses involved a number of comparisons, increasing the chance for type I error. However, the pattern of results, while nuanced, was relatively convergent on the role of negative emotions in the informed consent process—particularly with respect to comparisons between fear and anger, as predicted. Thus, although multiple comparisons increases the probability that effects will be detected because of chance, such chance results should be more randomly distributed rather than converging on a general pattern.

These limitations are offset by a number of strengths. This is the first study to systematically and experimentally examine fundamental psychological mechanisms that may explain deficits in the informed consent process for cancer clinical trials. Our study included a diverse community sample and focused on negative emotions (sadness, fear, and anger) commonly experienced in conjunction with cancer. Moreover, the induction of emotions enhanced internal validity by separating emotion from the stimulus (i.e., the consent form).

One important implication of this study is that negative emotions may sometimes impede the informed consent process. Our findings suggest that fear may result in lower ability to understand or recall information provided in the consent documentation, as evidenced by reduced recall of information provided in the consent form. Moreover, anger triggered less systematic processing of the consent form and related visual attention patterns; in turn, those who were angry and processed information less systematically were *more* likely to participate. This is potentially problematic, given the imperative that volunteers in clinical trials should participate with full understanding of risks and consequences (Faden & Beauchamp, 1986). Research is needed to develop

interventions that counter the deleterious effect of negative emotional states on the informed consent process or to refine existing efforts to improve understanding or attenuate the influence of emotion on decisions. For example, interventions designed to reduce negative emotions in cancer (Fors et al., 2011; Ross et al., 2002) may also be appropriate for facilitating understanding of clinical trial consenting information. Another strategy for mitigating the effects of emotion on the informed consent process may be to simply inform potential volunteers that their emotions may influence the way they process the document and make their decision; research has demonstrated that one robust boundary condition for the effects of emotion on judgment and decision making is awareness of the potential influence of emotions (Han et al., 2007). Finally, because existing interventions to improve the informed consent process are resource and cost-intensive (Flory & Emanuel, 2004), making them difficult to employ on a large scale, there is great utility in identifying individuals who might be in particular need of extra intervention in the context of informed consent. Thus, clinical trial researchers could facilitate informed consent by identifying those at increased risk for misunderstanding or bias by administering emotional assessments.

REFERENCES

- Andrade, E. B., & Ariely, D. (2009). The enduring impact of transient emotions on decision making. *Organizational Behavior and Human Decision Processes*, *109*(1), 1–8.
- Angie, A. D., Connelly, S., Waples, E. P., & Kligyte, V. (2011). The influence of discrete emotions on judgment and decision-making: A meta-analytic review. *Cognition & Emotion*, *25*(8), 1393–1422. DOI: 10.1080/02699931.2010.550751
- Appelbaum, P. S., Lidz, C. W., & Grisso, T. (2004). Therapeutic misconception in clinical research: Frequency and risk factors. *IRB: Ethics & Human Research*, *26*, 1–8.
- Arora, A., Rajagopalan, S., Shafiq, N., Pandhi, P., Bhalla, A., Dhibar, D. P., & Malhotra, S. (2011). Development of tool for the assessment of comprehension of informed consent form in healthy volunteers participating in first-in-human studies. *Contemporary Clinical Trials*, *32*, 814–817. DOI: 10.1016/j.cct.2011.05.012
- Barracough, J. (1999). *Cancer and emotion: A practical guide to psycho-oncology* (3rd ed.). West Sussex, England: John Wiley & Sons Ltd.
- Bergamin, J., Johansson, H., & Wilking, N. (2011). Levels of knowledge and perceived understanding among participants in cancer clinical trials—Factors related to the informed consent procedure. *Clinical Trials*, *8*, 77–84.
- Bergenmar, M., Molin, C., Wilking, N., & Brandberg, Y. (2008). Knowledge and understanding among cancer patients consenting to participate in clinical trials. *European Journal of Cancer*, *44*, 2627–2633.
- Bill, T. D. (1980). *My bodyguard* [Motion picture]. USA: Twentieth Century Fox.
- Brody, B. A., McCullough, L. B., & Sharp, R. R. (2005). Consensus and controversy in clinical research ethics. *Journal of the American Medical Association*, *294*, 1411–1414.
- Bodenhausen, G. V., Sheppard, L. A., & Kramer, G. P. (1994). Negative affect and social judgment: The differential impact of anger and sadness. *European Journal of social psychology*, *24*(1), 45–62.
- Brown, R. F., Butow, P. N., Ellis, P., Boyle, F., & Tattersall, M. H. N. (2004). Seeking informed consent to cancer clinical trials:

- Describing current practice. *Social Science & Medicine*, 58, 2445–2457.
- Carver, C. S., & Harmon-Jones, E. (2009). Anger is an approach-related affect: evidence and implications. *Psychological bulletin*, 135(2), 183.
- Chaiken, S., & Eagly, A. H. (1989). Heuristic and systematic information processing within and beyond the persuasion context. In J. S. Uleman, & J. A. Bargh (Eds.), *Unintended thought*. New York: Guilford.
- Collyar, D. E. (2000). The value of clinical trials from a patient perspective. *The Breast Journal*, 6(5), 310–314. DOI: 10.1046/j.1524-4741.2000.20060.x
- Cox, K., & McGarry, J. (2003). Why patients don't take part in cancer clinical trials: An overview of the literature. *European Journal of Cancer Care*, 12(2), 114–122. DOI: 10.1046/j.1365-2354.2003.00396.x
- Daugherty, C., Ratain, M. J., Grochowski, E., Stocking, C., Kodish, E., Mick, R., & Siegler, M. (1995). Perceptions of cancer patients and their physicians involved in phase I trials. *Journal of Clinical Oncology*, 13, 1062–1072.
- Davis, T. C., Berkel, H. J., & Holcombe, R. F. (1998). Informed consent for clinical trials: A comparative study of standard versus simplified forms. *Journal of the National Cancer Institute*, 90, 668–674.
- Demme, J. D. (1991). *Silence of the lambs [Motion picture]*. USA: Orion Pictures.
- Ding, E. L., Powe, N. R., Manson, J. E., Sherber, N. S., & Braunstein, J. B. (2007). Sex differences in perceived risks, distrust, and willingness to participate in clinical trials. *Archives of Internal Medicine*, 167, 905–912.
- Faden, R. R., & Beauchamp, T. L. (1986). *A history and theory of informed consent*. New York, NY: Oxford University Press.
- Ferrer, R. A., Klein, W. M. P., Lerner, J. S., Reyna, V., & Keltner, D. (in press). Emotions and health decision making: Extending the appraisal tendency framework to improve health and health care. To appear in C. Roberto, & I. Kawachi (Eds.), *Behavioral economics and public health*. New York, NY: Oxford University Press.
- Fessler, D. M. T., Pillsworth, E. G., & Flanson, T. J. (2004). Angry men and disgusted women: An evolutionary approach to the influence of emotions on risk taking. *Organizational Behavior and Human Decision Processes*, 95(1), 107–123. DOI: 10.1016/j.obhdp.2004.06.006
- Flory, J., & Emanuel, E. (2004). Interventions to improve research participants' understanding in informed consent for research: A systematic review. *Journal of the American Medical Association*, 292, 1593–1601.
- Ford, B. M., Evans, J. S., Stoffel, E. M., Balmana, J., Regan, M. M., & Syngal, S. (2006). Factors associated with enrollment in cancer genetics research. *Cancer Epidemiology, Biomarkers and Prevention*, 15, 1355–1359.
- Ford, B. Q., Tamir, M., Brunyé, T. T., Shirer, W. R., Mahoney, C. R., & Taylor, H. A. (2010). Keeping your eyes on the prize: anger and visual attention to threats and rewards. *Psychological Science*, 21(8), 1098–1105.
- Fors, E. A., Bertheussen, G. F., Thune, I., Juvet, L. K., Elvsaas, I. K. Ø, Oldervoll, L., ... & Leivseth, G. (2011). Psychosocial interventions as part of breast cancer rehabilitation programs? Results from a systematic review. *Psycho-Oncology*, 20(9), 909–918.
- Frijda, N. H. (1986). *The emotions*. Cambridge University Press.
- Gross, J. J., & Levenson, R. W. (1995). Emotion elicitation using films. *Cognition & Emotion*, 9(1), 87–108.
- Grossman, M., & Wood, W. (1993). Sex differences in intensity of emotional experience: A social role interpretation. *Journal of Personality and Social Psychology*, 65, 1010–1022.
- Han, S., Lerner, J. S., & Keltner, D. (2007). Feelings and consumer decision making: The appraisal-tendency framework. *Journal of Consumer Psychology*, 17(3), 158–168. DOI: 10.1016/s1057-7408(07)70023-2
- Hardesty, T. D. (1997). *Alaska's wild Denali [Motion picture]*. USA: Alaska Video Postcard.
- Hoffman, E. A., & Subramaniam, B. (1995). The role of visual attention in saccadic eye movements. *Perception & Psychophysics*, 57, 787–795.
- Isaacowitz, D. M., Toner, K., Goren, D., & Wilson, H. (2008). Looking while unhappy: Mood congruent gaze in younger adults, positive gaze in older adults. *Psychological Science*, 19, 848–853. DOI: 10.1111/j.1467-9280.2008.02167.x
- Jagsi, R., Motomura, A. R., Amarnath, S., Jankovic, A., Sheets, N., & Ubel, P. A. (2009). Under-representation of women in high-impact published clinical cancer research. *Cancer*, 115, 3293–3301.
- Jansen, L. A., Appelbaum, P. S., Klein, W. M. P., Weinstein, N. D., Cook, W., Fogel, J. S., & Sulmasy, D. P. (2011). Unrealistic optimism in early-phase oncology trials. *IRB: Ethics & Human Research*, 33(1), 1–8.
- Jefford, M., & Moore, R. (2008). Improvement of informed consent and the quality of consent documents. *Lancet Oncology*, 8, 485–493.
- Jenkins, V., Fallowfield, L., Souhami, A., & Satwell, M. (1999). How do doctors explain randomised clinical trials to their patients? *European Journal of Cancer*, 35, 1187–1193.
- Just, M. A., & Carpenter, P. A. (1980). A theory of reading: From eye fixations to comprehension. *Psychological Review*, 87, 329–354.
- Kliegl, R., Grabner, E., Rolfs, M., & Engbert, R. (2004). Length, frequency, and predictability effects of words on eye movements in reading. *European Journal of Cognitive Psychology*, 16, 262–284.
- Kuo, F.-Y., Hsu, C.-W., & Day, R.-F. (2009). An exploratory study of cognitive effort involved in decision under framing—An application of the eye-tracking technology. *Decision Support Systems*, 48(1), 81–91. DOI: 10.1016/j.dss.2009.06.011
- Lench, H., Flores, S., & Bench, S. (2011). Discrete emotions predict changes in cognition, judgment, experience, behavior, and physiology: A meta-analysis of experimental emotion elic. *Psychological Bulletin*, 137, 834–855.
- Lerner, J. S., Gonzalez, R. M., Small, D. A., & Fischhoff, B. (2003). Effects of fear and anger on perceived risks of terrorism: A national field experiment. *Psychological Science*, 14(2), 144–150. DOI: 10.1111/1467-9280.01433
- Lerner, J. S., & Keltner, D. (2000). Beyond valence: Toward a model of emotion-specific influences on judgement and choice. *Cognition and Emotion*, 14(4), 473–493. DOI: 10.1080/026999300402763
- Lerner, J. S., & Keltner, D. (2001). Fear, anger, and risk. *Journal of Personality and Social Psychology*, 81(1), 146–159. DOI: 10.1037/0022-3514.81.1.146
- Lerner, J. S., Small, D. A., & Loewenstein, G. (2004). Heart strings and purse strings carryover effects of emotions on economic decisions. *Psychological Science*, 15(5), 337–341.
- Lerner, J. S., & Tiedens, L. Z. (2006). Portrait of the angry decision maker: How appraisal tendencies shape anger's influence on cognition. *Journal of Behavioral Decision Making*, 19(2), 115–137.
- Li, T., Fung, H. H., & Isaacowitz, D. M. (2011). The role of dispositional reappraisal in the age-related positivity effect. *Journals of Gerontology: Psychological Sciences and Social Sciences*, 66B, 56–60. DOI: 10.1093/geronb/gbq074
- Lighthall, N. R., Mather, M., & Gorlick, M. A. (2009). Acute stress increases sex differences in risk seeking in the balloon analogue risk task. *PLoS One*, 4, e6002.
- Mather, M., & Lighthall, N. R. (2012). Risk and reward are processed differently in decisions made under stress. *Current Directions in Psychological Science*, 21, 36–41.
- Mills, E. J., Seely, D., Rachlis, B., Griffith, L., Wu, P., Wilson, K., ... Wright, J. R. (2006). Barriers to participation in clinical trials of cancer: A meta-analysis and systematic review of patient-reported factors. *The Lancet Oncology*, 7(2), 141–148. DOI: 10.1016/s1470-2045(06)70576-9

- Mogg, K., Bradley, B. P., Field, M., & De Houwer, J. (2003). Eye movements to smoking-related pictures in smokers: Relationship between attentional biases and implicit and explicit measures of stimulus valence. *Addiction*, *98*, 825–836. DOI: 10.1046/j.1360-0443.2003.00392.x
- Murthy, V. H., Krumholz, H. M., & Gross, C. P. (2004). Participation in cancer clinical trials: Race-, sex-, and age-based disparities. *Journal of the American Medical Association*, *291*, 2720–2726.
- Moons, W. G., & Mackie, D. M. (2007). Thinking straight while seeing red: The influence of anger on information processing. *Personality and Social Psychology Bulletin*.
- Parker, M. T., & Isbell, L. M. (2010). How I vote depends on how I feel: The differential impact of anger and fear on political information processing. *Psychological Science*, *21*(4), 548–550. DOI: 10.1177/0956797610364006
- Penman, D. T., Holland, J. C., Bahna, G. F., Morrow, G., Schmale, A. H., Derogatis, L. R., ... Cherry, R. (1984). Informed consent for investigational chemotherapy: patients' and physicians' perceptions. *Journal of Clinical Oncology*, *2*, 849–855.
- Posner, M. I., Snyder, C. R., & Davidson, B. J. (1980). Attention and the detection of signals. *Journal of Experimental Psychology: General*, *109*, 160–174. DOI: 10.1037/0096-3445.109.2.160
- Radach, R., Huestegge, L., & Reilly, R. (2008). The role of global top-down factors in local eye-movement control in reading. *Psychological Research*, *72*, 675–688.
- Rayner, K. (1998). Eye movements in reading and information processing. *Psychological Bulletin*, *124*, 372–422. DOI: 10.1037//0033-2909.124.3.372
- Rayner, K., & Fischer, M. H. (1996). Mindless reading revisited: Eye movements during reading and scanning are different. *Perception & Psychophysics*, *58*, 734–747.
- Rayner, K., Reichle, E. D., Stroud, M. J., Williams, C. C., & Pollatsek, A. (2006). The effect of word frequency, word predictability, and font difficulty on the eye movements of young and older readers. *Psychology and Aging*, *21*, 448–465. DOI: 10.1037/0882-7974.21.3.448
- Rodenhuis, S., van den Heuvel, W. J., Annyas, A. A., Koops, H. S., Sleijfer, D. T., & Mulder, N. H. (1984). Patient motivation and informed consent in a phase I study of an anticancer agent. *European Journal of Cancer & Clinical Oncology*, *20*, 457–462.
- Rottenberg, J., Ray, R., & Gross, J. J. (2007). Emotion elicitation using films. In J. Coan, & J. Allen (Eds.), *Handbook of emotion elicitation and assessment* (pp. 9–28). New York, NY: Oxford University Press.
- Ross, L., Boesen, E. H., Dalton, S. O., & Johansen, C. (2002). Mind and cancer: does psychosocial intervention improve survival and psychological well-being?. *European Journal of Cancer*, *38*(11), 1447–1457.
- Salojärvi, J., Puolamäki, K., Simola, J., Kovanen, L., Kojo, I., & Kaski, S. (2005). Inferring relevance from eye movements: Feature extraction. *Helsinki University of Technology*.
- Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, *103*, 403–428. DOI: 10.1037/0033-295X.103.3.403
- Stanton, A. L., Danoff-burg, S., & Huggins, M. E. (2002). The first year after breast cancer diagnosis: Hope and coping strategies as predictors of adjustment. *Psycho-Oncology*, *11*, 93–102. DOI: 10.1002/pon.574
- Stanton, A. L., & Snider, P. R. (1993). Coping with a breast cancer diagnosis: A prospective study. *Health Psychology*, *12*, 16–23.
- Tiedens, L. Z., & Linton, S. (2001). Judgment under emotional certainty and uncertainty: The effects of specific emotions on information processing. *Journal of Personality and Social Psychology*, *81*(6), 973–988. DOI: 10.1037/0022-3514.81.6.973
- Velichkovsky, B. M. (1999). From levels of processing to stratification of cognition: Converging evidence from three domains of research. *Stratification in cognition and consciousness*, *15*, 203.
- Velichkovsky, B. M., Rothert, A., Kopf, M., Dornhöfer, S. M., & Joos, M. (2002). Towards an express-diagnostics for level of processing and hazard perception. *Transportation Research Part F: Traffic Psychology and Behaviour*, *5*, 145–156. DOI: 10.1016/S1369-8478(02)00013-X
- Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology*, *54*, 1063–1070. DOI: 10.1037/0022-3514.54.6.1063
- Weary, G., & Jacobson, J. A. (1997). Causal uncertainty beliefs and diagnostic information seeking. *Journal of Personality and Social Psychology*, *73*(4), 839.
- Zeffirelli, F. (1979). *The champ [Motion picture]*. USA: Metro-Goldwyn-Mayer.

Authors' biographies:

Rebecca A. Ferrer, PhD, earned her doctoral degree in Social Psychology at the University of Connecticut. She is presently a health scientist/ program director in the Basic Biobehavioral and Psychological Sciences Branch within the Division of Cancer Control and Population Science's Behavioral Research Program at the National Cancer Institute.

Jennifer Tehan Stanley, PhD, earned her doctoral degree in Experimental Psychology from The Georgia Institute of Technology. She is currently an assistant professor of Psychology at The University of Akron.

Kaitlin Graff earned a Bachelor of Arts in Psychology from Kenyon College. Currently, she is in a dual masters program at Washington University in St. Louis where she is studying social work and public health.

William Klein earned his doctoral degree in social psychology at Princeton University in 1991. He is currently the associate director of the Behavioral Research Program at the National Cancer Institute, and an adjunct investigator in the Social and Behavioral Research Branch of the National Human Genome Research Institute.

Nina Goodman, MHS, earned her Masters of Health Science at Johns Hopkins Bloomberg School of Public Health. She is currently the branch chief of Internal Communications within the Office of Communications and Public Liaison at the National Cancer Institute.

Wendy L. Nelson, PhD, earned her doctoral degree in Clinical Psychology at Saint Louis University. She is presently a health specialist/program director in the Basic Biobehavioral and Psychological Sciences Branch, within the Division of Cancer Control and Population Science's Behavioral Research Program at the National Cancer Institute.

Silvia Inez Salazar earned her master's degree in Public Administration from Baruch College. She is currently Informatics Research Lab Manager in the Office of Communications and Public Liaison at the National Cancer Institute.

Authors' addresses:

Rebecca A. Ferrer, National Cancer Institute, Rockville, MD, USA.

Kaitlin Graff, National Cancer Institute, Rockville, MD, USA.

William M. P. Klein, National Cancer Institute, Rockville, MD, USA.

Nina Goodman, National Cancer Institute, Rockville, MD, USA.

Wendy L. Nelson, National Cancer Institute, Rockville, MD, USA.

Jennifer Tehan Stanley, University of Akron, Akron, OH, USA.