#### **BLOOD DONORS AND BLOOD COLLECTION**

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# TRANSFUSION

# Predicting vasovagal reactions to a virtual blood donation using facial image analysis

Judita Rudokaite<sup>1,2</sup> | Lee-Ling Sharon Ong<sup>1</sup> | Mart P. Janssen<sup>2</sup> | Eric Postma<sup>1</sup> | Elisabeth Huis in 't Veld<sup>1,2</sup>

<sup>1</sup>Department of Cognitive Science and Artificial Intelligence, Tilburg University, Tilburg, the Netherlands

<sup>2</sup>Department of Donor Medicine Research, Sanquin, Amsterdam, the Netherlands

#### Correspondence

Judita Rudokaite, Department of Cognitive Science and Artificial Intelligence, Tilburg University, Tilburg, the Netherlands. Email: j.rudokaite@tilburguniversity.edu

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#### Abstract

**Background:** People with needle fear experience not only anxiety and stress but also vasovagal reactions (VVR), including nausea, dizziness, sweating, pallor changes, or even fainting. However, the mechanism behind needle fear and the VVR response are not yet well understood. The aim of our study was to explore whether fluctuations in facial temperature in several facial regions are related to the level of experienced vasovagal reactions, in a simulated blood donation.

**Study design and methods:** We recruited 45 students at Tilburg University and filmed them throughout a virtual blood donation procedure using an Infrared Thermal Imaging (ITI) camera. Participants reported their fear of needles and level of experienced vasovagal reactions. ITI data pre-processing was completed on each video frame by detecting facial landmarks and image alignment before extracting the mean temperature from the six regions of interest.

**Results:** Temperatures of the chin and left and right cheek areas increased during the virtual blood donation. Mixed-effects linear regression showed a significant association between self-reported vasovagal reactions and temperature fluctuations in the area below the nose.

**Discussion:** Our results suggest that the area below the nose may be an interesting target for measuring vasovagal reactions using video imaging techniques. This is the first in a line of studies, which assess whether it is possible to automatically detect levels of fear and vasovagal reactions using facial imaging, from which the development of e-health solutions and interventions can benefit.

#### KEYWORDS

needle fear, thermal imaging, vasovagal reactions

### **1** | INTRODUCTION

There is strong evidence to suggest that needle fear is an important risk factor for vasovagal reactions,<sup>1–5</sup> which

includes being nauseous, dizzy, lightheaded, sweaty, pale, or even vomiting or fainting. Needle fear is a common issue, prevalent among 20%-50% in adolescents and 20%-30% in young adults.<sup>6</sup> France et al  $(2014)^5$  reported

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that fear of needles was the strongest predictor of vasovagal reactions, even after controlling for other individual predictors such as sex, age, and body mass index.<sup>5,7–10</sup>

In blood banking, several interventions or strategies have been tested to help donors cope with tension and the possibility of experiencing a VVR, such as distraction, water loading, or applied muscle tension (AMT) before and during the venipuncture.<sup>11</sup> Unfortunately, these interventions only work for a subset of donors,<sup>12</sup> possibly because they do not address the psychological components that play a role. During stressful events, the sympathetic Autonomic Nervous System (ANS) is activated which results in physiological changes such as an increased heart-rate<sup>13</sup> or changes in breathing pattern.<sup>14,15</sup> Hoogerwerf et al (2018; 2017)<sup>16,17</sup> found that psychological, hormonal, and psychophysiological stress markers slowly increased in anticipation of the needle insertion, at which time they peak. Unfortunately, these psychophysiological responses are automatic and difficult to self-report, which makes them difficult targets for in an intervention. However, they can be measured using only psychophysiological techniques. Therefore, we propose an innovative and non-invasive technique to measure and predict vasovagal reactions: Infrared Thermal Imaging (ITI). ITI is a novel technique for affective computing and measuring an individual's psychophysiological states. Related work has shown that psychological stress levels could be predicted from their breathing patterns using thermal imaging<sup>18</sup> or measured in real-time from increased blood flow in the frontal vessel of the forehead.<sup>19</sup> Furthermore, emotions or psychological states could be also predicted by temperature changes at specific areas of the face.<sup>20,21</sup> For example, a decrease in temperature of the nose tip is associated with increased stress levels.<sup>21</sup> This inspired the FAcial INfrared Thermal imaging in the prevention of needle-induced fainting (FAINT) project, with the aim of developing an Artificial Intelligence algorithm able to predict needle-induced fear and VVR responses from facial imaging.

To mimick a blood draw in the lab, we induced emotional reactions to needle exposure using a virtual blood donation experiment. This experimental design is based on the "rubber hand illusion",<sup>22</sup> a well-known method to induce the feeling of ownership of, as the name implies, a fake limb such as a rubber arm.<sup>23</sup> Using this paradigm, it was found that the sight of a needle 'threatening' the fake arm resulted in neurological processes relating to anxiety, interoception, and motor control (e.g., the urge to withdraw the arm).<sup>24</sup> Trost (2017)<sup>25</sup> developed a videobased blood donation based on this paradigm and showed that this indeed caused significant physiological changes in respiration, blood pressure, and skin conductance. Hence, the aim of this first explorative study of the FAINT project is to assess changes in facial temperature using an infrared thermal imaging camera during a 'virtual' blood donation.

#### 2 | METHODS AND MATERIALS

#### 2.1 | Procedure

The participants were recruited via cloud-based participant management software (SONA) at Tilburg University. Participants were asked not to wear glasses during thermographic shots, and to be free from nicotine and caffeine at least 3 h prior to the study. The room temperature was T = 21.84 °C (SD = 1.55), and the relative humidity was H = 42.54% (SD = 3.15%). The experiment was approved by the Research Ethics and Data Management Committee of Tilburg School of Humanities and Digital Sciences (Approval Letter: 2019/72).

On arrival, participants were given the first questionnaire, containing items regarding demographic variables. After the subjects completed the questionnaire, we assessed baseline VVR levels (see Section 2.4) and started a baseline thermal imaging recording (T = 2–5 min), with the participants in rest. Then, participants were exposed to the experiment; a virtual blood donation. This experiment is a virtual version of the Rubber Arm Illusion<sup>25</sup> and we repeat the experimental setup and stimuli from Trost et al. (2017).<sup>25</sup> Finally, we asked participants to again rate their VVR responses and to complete a second questionnaire.

Thermal imaging of the patients was carried out using the FLIR E95 camera with thermal sensitivity of <40 mK at 30°C, an infrared resolution of 464 x 348 pixels. The camera was installed on a tripod at a distance of about 1 meter from the subject. The camera captured 30 frames per second.

#### 2.2 | Experimental stimuli

The stimuli of the virtual blood donation were provided by Trost et al. (2017).<sup>25</sup> The videos showed an arm placed on a table (see Trost et al.  $(2017)^{25}$ ), palm up. Several videos were available showing either a left or a right arm of a female or male donor in several skin tones. The video consisted of 5 phases. In the first phase, the arm on the screen is stroked with a brush, and the fingers are tapped with the back of the brush. Next, the video would show a needle placed next to the arm, followed by an alcohol swab. Finally, a needle was inserted, and a blood draw would take place that lasted 5 min and 3 s.

### 2.3 | Study design

The study has a 2 between factor (experimental, control) by 6 within factor (time) design. The participants were randomly assigned to the experimental or the control group. In the experimental group, the rubber arm illusion was induced through synchronous stroking of the real arm in line with the arm on the screen. As the participant sees and feels the same, this induces the rubber arm illusion, causing the brain to incorporate the arm on the screen into the body schema, and acting as if the arm on the screen is the own arm. In the control condition, the illusion was not induced, as the real arm of the participant was stroked and tapped with a few seconds delay. This asynchronicity significantly reduces the effect of the illusion.

Apart from this condition, the experiment was identical for all subjects. The data was divided into six-time segments (see Section 2.5). Six facial regions were selected based on previous studies<sup>20,21,26</sup> – the region between the eyes (forehead), tip of the nose, area below the nose, chin, and both cheeks. We hypothesize that temperature patterns will differ among individuals who experience different vasovagal reactions.

#### 2.4 | Measures

#### 2.4.1 | Demographic variables

Before the experiment, participants were asked to report demographic variables including gender (0 = male, 1 = female), age, previous donation experience (0 = none, 1 = 1-2 times, 2 = 3-5 times, 3 = 6-10 times, 4 = morethan 10 times), fear of needles (0 = no, 1 = yes), and if they ever experienced any given vasovagal reactions during any needle related procedure (0 = no, 1 = yes; based on BDRI<sup>27</sup>).

#### 2.4.2 | Vasovagal reactions

After the experiment, participants rated the extent to which they experienced VVRs using the Blood Donation Reactions Inventory (BDRI<sup>27</sup>). This is a questionnaire consisting of 11 items on which participants are asked to rate faintness, dizziness, weakness, lightheadedness, facial flush, visual disturbance, rapid or pounding heart, difficulty hearing, sweating, nausea, rapid or difficulty breathing on the Likert scale from 0 (not at all) to 5 (extremely) before and after the virtual blood donation. The maximum score was 55 points, and the higher the score, the higher the degree of presyncopal reactions; Cronbach  $\alpha = 0.835$ .

# 2.4.3 | Rubber-hand illusion questionnaire (RHI; based on<sup>22,28</sup>)

Lastly, the participants completed the RHI, used to assess the extent to which the illusion was successfully induced. Participants were asked to report their subjective experience with regards to arm ownership. The scale was divided into 2 subscales, one pertaining to ownership (e.g., "It seemed as if I was feeling the touch at the location where I saw the brush touch my arm", Cronbach  $\alpha = 0.866$ ) and the other serving as a control, e.g., "I felt as if my real hand was turning rubbery" (ownership control). The control statements should be answered negatively, and serve to check whether the participant is answering reliably. The questions were rated on a 7-point Likert scale ranging from -3 (totally disagree) to 3 (totally agree), and each subscale consisted of the mean scores of 4 questions. The RHI also includes an 'agency' component, which does not apply to this study, as the participants do not move their own or the virtual arm.

#### 2.5 | Data pre-processing

Thermal videos were recorded in raw (.sql) format, which means that all temperature values at each video frame were obtained. We used the FLIR Research IR tool to export the thermal files. For each frame, we exported a visual representation and the raw temperature values for post-processing. For each participant, the start of the virtual blood donation (when the button on the computer screen was pressed and prerecorded videos started playing) was identified. As each prerecorded video file had the same length, we selected 3202 frames for each participant for further analysis. The needle was inserted at frame 1771.

To extract the mean temperature values from specific regions of interest, we completed a three-step image preprocessing explained in Figure 1. Then, we extracted the mean temperature value from each ROI at each frame for each participant. Finally, for each participant we divided the recording of 3202 frames (corresponding to 107 s) into six parts to have six intervals for data analysis:

- a. a baseline, prior to the virtual blood draw, which resulted in 600 frames (20 s);
- b. before the needle was inserted; 600 frames;

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Image (A) An original thermal image.

Image (B) An estimation of facial landmarks.



Image (C) A representation of the aligned image that fits the frontal template.

**FIGURE 1** An example of the process for automatically extracting temperature values from thermal recordings. Image A is an original thermal image, which was used for detecting the face and estimated the facial landmarks of each participant in order to track the face over time using the face alignment network (FAN)<sup>29</sup>). The FAN received a thermal image file as input and produce the corresponding 2D landmarks and 2D projections of the 3D landmarks as outputs (Image B represent the image after estimation of facial landmarks). Next, the images were aligned such that the features detected in one image would match the features in the other image and that all temperature values would be extracted from the same location. We aimed to have all frontal images, therefore, we selected a frontal reference image that served as our template. Then, we warped each thermal image to fit the template using the coordinates of the facial landmarks from both images. This was done using a warp affine transformation technique. Finally, we re-created each thermal image as a frontal one by pasting calculated triangles from our original image into our template image. The same procedure was completed for both a visual image and a raw temperature file. Image C represents the aligned image that fits the frontal template. The gray boxes in image C represent the six regions of interest where the mean temperature was extracted from: nose, below the nose, cheeks, chin, and the area between the eyes

- c. when the needle was presented on the screen to the participants; 400 frames (duration 13.3 s);
- d. when needle was inserted; 400 frames;
- e. just after needle insertion; 600 frames;
- f. when blood was drawn in the prerecorded video; 600 frames.

The average temperature values obtained for each timepoint were used for further statistical analysis.

#### 2.6 | Data analysis

To assess whether there are any differences in demographic composition with regards to gender and (previous) VVR experience and post-BDRI symptoms, two-tailed Fisher's exact tests and Mann-Whitney U tests were run. The extent to which the participants filled out the RHI reliably was assessed by comparing the scores on the two subscales (ownership vs. ownership control) using a non-parametric paired sample t-test. Additionally, the extent to which the illusion was induced more strongly in the experimental group was tested by comparing the ownership scores across conditions using a nonparametric independent-samples t-test. A mixed-effects linear regression model<sup>30</sup> was applied separately for each ROI with mean temperature as the dependent variable with post-experiment BDRI score, six timepoints, selfreported needle fear (yes/no) and the interaction between

post-experiment BDRI score and self-reported needle fear as independent variables. For further analysis, we selected only those models that had statistically significant main effects, which means that they were a better fit than a null model. Deviations from the normal distribution were verified by applying the Shapiro–Wilk test. Questionnaire data were analyzed using RStudio<sup>31</sup> and SPSS.<sup>32</sup> All the tests were two-tailed and the null hypothesis was rejected at a 5% significance level.

#### 3 | RESULTS

#### 3.1 | Participants

Forty-five participants (37 females) participated in the study. There were no significant differences in baseline characteristics between participants in the experimental and the control group (Table 1). There was also no difference in the number of participants suffering from needle fear between the control and experimental groups.

### 3.2 | Self-reported fear of needles

Table 2 shows that were no differences in demographic composition between participants who indicated to be scared of needles (n = 22) and those who reported not to be (n = 23; see Table 2). However, participants with

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control group	(who received asynchronal stimulation; $n = 19$ )
FABLE 1	Differences in characteristics of participants in the experimental group (who received synchronal stimulation; $n = 26$ ) and

		Experimental group M/n	SD/%	Control group M/n	SD	T/χ²/U statistic	р
Gender <sup>a</sup>	Male	5		3			.99
	Female	21		16			
Age		21.81	3.62	22.74	5.98	t = -0.648	.521
BMI		21.36	2.24	22.26	3.03	t = -1.142	.260
Needle fear	No	14		9			.767
	Yes	12		10			
Blood donation	None	18		16		$\chi^{2}(2) = 1.851$	.396
experience	1–2	7		2			
	3-5	1		1			
Previous VVR experience		2.85	2.27	2.37	2.83	U = 196.5	.236
Post-experiment BDRI		21.19	8.16	20.53	8.26	U = 219.5	.526

Note: VVR is the average total number of previously experienced vasovagal reactions.

Abbreviations: BMI, body mass index, BDRI, blood donation reaction inventory sumscore.

<sup>a</sup>Result of a two tailed Fisher's exact test.

**TABLE 2** Differences between participants who self-reported to suffer from needle fear (n = 22) and who reported not to suffer from needle fear (n = 23)

		Needle fear group M/n	SD/%	Non needle fear group M/n	SD	T/χ²/U statistic	р
Gender <sup>a</sup>	Male	2		6			.243
	Female	20		17			
Age		22.41	4.49	22.0	5.03	t = -0.287	.775
BMI		21.08	2.8	21.67	2.48	t = -0.168	.868
Blood donation experience	None	17		17		$\chi^{2}(2) = 0.089$	.957
	1–2	4		5			
	3–5	1		1			
Previous VVR experience		2.86	2.95	2.43	2.04	U = 250.5	.954
Post-experiment BDRI		24.68	8.46	17.3	5.95	U = 1265	.004

Note: VVR is the average total number of previously experienced vasovagal reactions.

Abbreviations: BMI, body mass index; BDRI, blood donation reaction inventory sumscore.

<sup>a</sup>Result of a two tailed Fisher's exact test.

needle fear reported significantly higher post-experiment BDRI. Therefore, we included an interaction term between post-experiment BDRI score and self-reported needle fear in the further analysis. In addition, participants who were scared of needles had a slightly higher mean temperature in all facial areas in comparison to participants who reported not being scared of needles (Figure 2). No other significant differences were found between the experimental and control groups nor among participants who reported needle fear or not. Therefore, no other items were included in the further analysis.

### 3.3 | Experimental condition

We also examined if the illusion was successfully induced in the experimental group. As expected, RHI ownership was significantly higher than RHI ownership control in both the experimental (Wilcoxon Z test = 4.255, p < .001) and control groups (Wilcoxon Z test = -3.681, p < .001), showing that the participants completed the survey correctly.<sup>22,28</sup> However, the difference in RHI ownership scores between synchronous and asynchronous conditions was not statistically significant (Mann-



**FIGURE 2** Smoothed mean temperature observed at six facial regions during the virtual blood donation (N = 3202 frames) from two groups (1 = not scared of needles, 2 = scared of needles). The black vertical line is the time of needle insertion

Whitney U = 190, p = .190), which means that both groups experienced the illusion. Therefore, we did not include the experimental condition in the further analysis.

#### 3.4 | Mixed-linear regression models

#### 3.4.1 | Nose, below the nose, and eye region

No statistically significant main effects were found for the nose ( $\chi^2[11] = 9.78$ , p = .3) and the area between the eyes ( $\chi^2[11] = 10.86$ , p = .21). However, a model with the temperature measures of the area below the nose was statistically significant ( $\chi^2[9] = 12.88$ , p = .045) with statistically significant associations between below nose area temperature and the post-experiment BDRI score, but not for any time points (Table 3). This shows that the more temperature in the area below the nose increases, the higher the BDRI score is reported.

#### 3.4.2 | Cheek regions

A statistically significant main effect was found for the left cheek temperature ( $\chi^2[11] = 19.34$ , p = .01). The analyses showed a statistically significant association for time point six, but not for the post-experiment BDRI score,

self-reported fear, an interaction term between needle fear and post-experiment BDRI score, or other time points (Table 3). It means that the temperature significantly increases in the left cheek area at time point six – during the blood draw after the needle insertion in the pre-recorded video.

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Furthermore, a statistically significant main effect was found for the right cheek temperature  $(\chi^2[11] = 15.84, p = .04)$ . The analyses showed a statistically significant association for time point six, but not for the post-experiment BDRI score, self-reported fear, an interaction term between needle fear and post-experiment BDRI score, or other time points (Table 3). It means that the temperature significantly increases in the right cheek area at time point six – during the blood draw after the needle insertion in the pre-recorded video.

#### 3.4.3 | Chin region

A statistically significant main effect was found  $(\chi^2[11] = 40.22, p < .001)$ . The analyses showed a statistically significant association for time point five and time point six, but not for the post-experiment BDRI score, self-reported fear, an interaction term between needle fear and post-experiment BDRI score, or other time points (Table 3). It means that the temperature significantly increases in the chin area at time point five and six

**TABLE 3** A mixed-effects linear regression models for chin, cheek and below nose regions with the mean temperature values as dependent variable and post-experiment BDRI score, the six timepoints, self-reported needle fear (yes/no) and the interaction between post-experiment BDRI score and self-reported needle fear as independent variables

	Dependent variable	β	SE	t	95% CI	р
Chin area	Post-experimental BDRI score	0.029	0.023	1.28	[-0.016, 0.074]	.21
	Time point 2	-0.05	0.04	-1.24	[-0.14, 0.03]	.22
	Time point 3	-0.067	0.04	-1.51	[-0.15, 0.019]	.13
	Time point 4	-0.015	0.04	-0.35	[-0.1, 0.7]	.72
	Time point 5	0.097	0.044	2.22	[0.012, 0.18]	.028
	Time point 6	0.15	0.044	3.42	[0.006,0.23]	.0008
	Self-reported needle fear	0.9	0.65	1.398	[-0.3899, 2.199]	.17
	Interaction between self-reported fear and post-experiment BDRI score	-0.03	0.029	-1.08	[-0.09, 0.027]	.29
Left cheek area	Post-experimental BDRI score	0.005	0.03	0.16	[-0.058, 0.068]	.87
	Time point 2	-0.028	0.08	-0.35	[-0.18, 0.128]	.73
	Time point 3	-0.08	0.08	-0.99	[-0.235, 0.075]	.32
	Time point 4	-0.1	0.08	-1.25	[-0.255, 0.055]	.21
	Time point 5	0.02	0.08	0.29	[-0.13, 0.18]	.077
	Time point 6	0.2	0.08	2.5	[0.045, 0.36]	.013
	Self-reported needle fear	0.04	0.91	0.04	[-1.78, 1.85]	.97
	Interaction between self-reported fear and post-experiment BDRI score	0.12	0.04	0.29	[-0.07, 0.094	.79
Right cheek area	Post-experimental BDRI score	-0.008	0.03	-0.27	[-0.006, 0.05]	.79
	Time point 2	0.02	0.08	0.26	[-0.13, 0.17]	.79
	Time point 3	-0.06	0.08	-0.08	[-0.22, 0.01]	.42
	Time point 4	-0.034	0.08	-0.43	[-0.189, 0.12]	.67
	Time point 5	0.004	0.08	0.05	[-0.15, 0.16]	.95
	Time point 6	0.17	0.08	2.18	[0.02,0.33]	.03
	Self-reported needle fear	0.68	0.79	0.86	[-0.89, 2.25]	.395
	Interaction between self-reported fear and post-experiment BDRI score	-0.002	0.036	-0.06	[-0.07, 0.069]	.95
Below nose region	Post-experimental BDRI score	0.04	0.02	2.14	[0.0028, 0.078]	.038
	Time point 2	-0.02	0.06	-0.32	[-0.13, 0.09]	.75
	Time point 3	-0.05	0.06	-0.93	[-0.16, 0.058]	.35
	Time point 4	0.013	0.06	0.23	[-0.098, 0.124]	.82
	Time point 5	0.08	0.06	1.43	[-0.03, 0.19]	.16
	Time point 6	0.07	0.06	1.26	[-0.039, 0.18]	.21

- just after the needle insertion and during the blood draw in the pre-recorded video.

### 4 | DISCUSSION

In this study, we measured facial temperature fluctuations in several facial regions during a simulated blood donation experiment and investigated whether there is an association between the self-reported vasovagal reactions and the observed changes in temperature.

Firstly, we found that 25% of the male (2 out of 8) and 54% of the female (20 out of 37) participants reported being scared of needles. These prevalences are in line with the prevalences by McLenon<sup>6</sup> reported in the meta-analysis for this age group. Furthermore, we found that the group with needle fear suffered higher levels of vasovagal reactions after the experiment, which

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is also in line with the expectations and the previous literature.<sup>7,9,10</sup>

More importantly, we found a positive association between the level of vasovagal reactions and facial temperature in the area below the nose. Thus, our results suggest that this area would be the most indicative for predicting vasovagal reactions. The nasal area is usually proposed as a region for detecting breathing patterns as the temperature increases while breathing out and decreases while breathing in.<sup>33–37</sup> This is in line with the rationale that hyperventilation might contribute to anxious state development.<sup>38–41</sup> Furthermore, this corroborates the finding of Trost et al (2017),<sup>25</sup> who found an increase in the respiratory rate in this virtual blood donation paradigm. We aim to replicate this study with additional physiological measurements (including respiration) in order to further assess these associations.

Also, we found that temperatures in the chin and cheek areas increased after needle insertion, regardless of whether the participant suffered from needle fear. These temperature increases were observed only after 20–30 s after needle insertion. Previous studies show that facial temperature response may have latency as quick as 2 s after an unexpected auditory stimulus<sup>33</sup> or as slow as 20–30 s after the stressful stimuli such as mishap paradigm<sup>34</sup> or video clips,<sup>35</sup> which can start in the first 10 s,<sup>34</sup> but last up to 30–60 s.<sup>35</sup> Thus, our findings of significant temperature increase in the chin and cheeks areas are likely to be associated with a delayed thermal response after needle insertion. For future studies, this temporal pattern should be taken into account when analyzing the data.

In this study, besides grouping participants based on their self-reported status as someone suffering from needle fear, we aimed to assess whether it was possible to pry apart the effects of 'experiencing' a blood donation versus just seeing a blood donation, as we know that merely the sight of needles and blood is able to induce adverse emotional and physical responses.24,42-45 The aim was to induce a sense of ownership of the arm on which the blood donation was performed in one group (the experimental group) but not in the control group. We expected that the group in which the illusion was induced was more likely to show vasovagal reactions and temperature fluctuations. Unexpectedly, we found a successful induction of arm ownership in both the control and the experimental groups, rather than only in the experimental group. Possibly, the temporal incongruence between seeing and feeling the brush<sup>46,47</sup> was too short to induce the illusion, even though previous research shows that a delay as short as 300 ms should be sufficient.<sup>47,48</sup> However, there are individual differences in which temporal resolution optimizes the individual susceptibility to the illusion.<sup>49</sup> As some participants can still experience the illusion with longer delays up to 600 ms, it is unlikely that the delay was too long.<sup>50</sup> It is however more likely that the salience of the 'blood donation' scenario is so great that the illusion is enhanced for this paradigm specifically. As Trost<sup>25</sup> only performed the synchronous condition in order to induce the illusion and also found that this successfully induces the illusion, we cannot compare this finding to results from previous studies.

The study does suffer from some limitations. Not only was data collection cut short due to the coronavirus pandemic, thereby limiting the sample size, but university students are fully informed about the aim and setup of the study, making it likely that students suffering from very high levels of needle fear did not participate. Furthermore, it would have been ideal to control for the effect of gender and age in the results, something that wasn't possible in this study due to the low number of men in the sample, and the limited age range of students. As women and young people are more likely to suffer from VVR than men,<sup>51</sup> this could have biased the results as well. The limited sample size also prevented the use of deep learning algorithms, able to assess other important predictors of VVR (e.g., facial expressions, heart rate, and pallor) simultaneously. Additionally, the videos used in this experiment have a short time frame, suboptimal to predict VVRs in a very early stage or to capture the overall pattern of reactions prior to and during a whole blood donation process. Many of these limitations will be solved in our upcoming FAINT study, as we are almost ready with data collection at the national blood bank in the Netherlands (Sanquin), including infrared thermal imaging and regular video data of 300 blood donors throughout an actual blood donation procedure. Lastly, we are also assessing whether similar patterns can be detected in 'regular' video images, rather than ITI images. Detection of such patterns will then be implemented in our AINAR (Artificial Intelligence for Needle Anxiety Reduction) solution that uses automatic recognition of facial patterns in artificial intelligencedriven biofeedback game that will help donors and patients conquer their fear of needles in an independent way, prior to the donation.

In conclusion, our results corroborate that this experimental paradigm can indeed be used to induce emotional and physical reactions and that assessing temperature fluctuations in the face could be a feasible method of measuring VVR in a non-intrusive, contactless way.

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# CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

# ORCID

Judita Rudokaite D https://orcid.org/0000-0001-9427-8051

Lee-Ling Sharon Ong D https://orcid.org/0000-0002-4120-163X

Mart P. Janssen <sup>(D)</sup> https://orcid.org/0000-0002-1682-7817 Eric Postma <sup>(D)</sup> https://orcid.org/0000-0001-9627-1523 Elisabeth Huis in 't Veld <sup>(D)</sup> https://orcid.org/0000-0002-5180-5744

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