Figures and figure supplements

Alcoholism gender differences in brain responsivity to emotional stimuli

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Figure 1. Schematic of task presentation, and examples of stimuli. As described in the text, participants were shown pictures from the International Affective Picture System (Lang et al., 1988) and asked to report how the pictures made them feel (good, bad, or neutral). Note the pictures in this figure are not the exact pictures shown to participants from the International Affective Picture System as these are not to be made available online (https://csea.phhp.ufl.edu/media/iapsmessage.html). The erotic (https://www.flickr.com/photos/103039225@N05/14964085720) and happy (https://www.flickr.com/photos/moonjazz/2684228420) images are in the public domain and are reproduced here under a Public Domain Mark 1.0 licence (https://creativecommons.org/publicdomain/mark/1.0/). The gruesome (https://commons.wikimedia.org/wiki/File:Amputation_surgery_01.JPG) and neutral (https://commons.wikimedia.org/wiki/File:Herstal_Y1944_med_tiltbar_skjerm-1.JPG) images are in the public domain and are reproduced here under a CC0 1.0 Universal (CC0 1.0) Public Domain Dedication (https://creativecommons.org/publicdomain/zero/1.0/deed.en). The aversive image was taken from the National Archives Catalog (https://catalog.archives.gov/id/6366489) where it was made available with no restrictions on its use.

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Figure 1—figure supplement 1. Conceptual model of emotional integration and evaluation, adapted from Halgren and Marinković (1995), and informed more recently by results of a meta-analytic analysis by Riedel et al. (2018). Widespread and focal dynamic corticolimbic neural networks embody a broad scope of circuitries linked to distinct functional systems for amalgamating cognitive with feeling aspects of emotions: Attention and orientation to a salient stimulus occurs in insular, anterior cingulate, prefrontal, and posterior parietal cortices; Emotional event appraisal, integration, and evaluation (as influenced by the ongoing emotional context and the perceiver’s personality), takes place in posterior cingulate, orbital and medial prefrontal cortex, and other neocortical sites (e.g., fusiform gyrus and superior temporal sulcus), and limbic structures (hippocampus and amygdala); Volition and decisions, which determine response choice, are generated in cingulate, precentral, premotor, and supplementary cortices.

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Figure 2. Participants' characteristics and drinking measures. The boxplot represents participant characteristics. Appendix 1—table 1 shows the means, standard deviations, and significant differences. In the boxplot above, blue diamonds indicate mean values. Age, education, DHD, and LOS are expressed in years and DD is in ounces of ethanol per day (approximating daily drinks). LOS values were not applicable for two nonalcoholic control men and four nonalcoholic control women who reported never drinking. Abbreviations: DHD = Duration of Heavy Drinking (>21 drinks per week) in years; DD = Daily drinks; LOS = Length of sobriety in years. HRSD = Hamilton Rating Scale for Depression (Hamilton, 1960); VIQ = Wechsler Adult Intelligence Scale, 3rd ed. Verbal Intelligence Quotient; PIQ = Wechsler Adult Intelligence Scale, 3rd ed. Performance Intelligence Quotient; WMS_DMI = Wechsler Memory Scale, 3rd ed. Delayed (General) Memory Index.

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**Figure 3.** Percentage of behavioral ratings by condition, rating, group, and gender. The boxplot represents the significant condition x rating x group interaction, and the significant condition x rating x gender interaction, for percentage rating of the pictures $p<0.05$ (Appendix 1—table 3). The group interaction is most clearly evident for the difference in the good and neutral ratings of the erotic pictures, with the alcoholic participants rating the pictures good less frequently; other picture types were rated more similarly by both the alcoholic and control groups. The gender interaction indicated that men rated erotic pictures as good more frequently than women. Blue diamonds indicate mean values. *Figure 3—figure supplement 1* shows the reaction times. Abbreviations: ALC = Alcoholic participants; NC = Nonalcoholic Control participants.

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Figure 3—figure supplement 1. Reaction times of behavioral ratings by condition, rating, group, and gender. The boxplot represents the significant rating x gender interaction for reaction times of the pictures p<0.05 (Appendix 1—table 4). The difference in the good rating of the erotic pictures by alcoholics vs. nonalcoholic controls. The ratings for other conditions were qualitatively similar for alcoholics and nonalcoholic control subjects. Blue diamonds indicate mean values. Figure 3 shows the reaction times. ALC = alcoholic participants; NC = nonalcoholic control participants.

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Figure 4. Erotic vs. neutral stimuli elicited abnormal activation of the limbic system and cerebellum in alcoholic men. A significant group x gender interaction in response to erotic vs. neutral stimuli was identified and is displayed as a green outline indicated by arrows. All inferior arrows designate the amygdala. Group mean contrast values are displayed in the four brain images located in the corners of the figure, and group comparisons are indicated by minus signs. Contrast values are overlaid on coronal cross sections. Images are displayed in radiological convention with the right hemisphere shown on the left. (Sagittal and axial views are shown in Figure 4—figure supplement 1 and Figure 4—figure supplement 2. Figure 4—figure supplement 3 shows the magnitude of cluster differences.) Abbreviations: ALCM = Alcoholic men; ALCW = Alcoholic women; NCWM = Nonalcoholic men; NCW = Nonalcoholic women.

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Figure 4—figure supplement 1. Erotic vs. neutral stimuli elicited abnormal activation of the limbic system and cerebellum in alcoholic men (sagittal view). A group x gender interaction in response to erotic vs. neutral stimulation was identified and is displayed as a green outline. Group mean values are displayed in the four brain images located in the corners of the figure, and group comparisons are indicated by minus signs. Contrast effect sizes are overlaid on sagittal cross sections. (Coronal and axial views are shown in Figure 4 and Figure 4—figure supplement 2; Figure 4—figure supplement 3 shows the magnitude of cluster differences.) Abbreviations: ALC_M = alcoholic men; ALC_W = alcoholic women; NC_M = nonalcoholic men; NC_W = nonalcoholic women.

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Figure 4—figure supplement 2. Erotic vs. neutral stimuli elicited abnormal activation of the limbic system and cerebellum in alcoholic men (axial view). A group x gender interaction in response to erotic vs. neutral stimulation was identified and is displayed as a green outline. Group mean values are displayed in the four brain images located in the corners of the figure, and group comparisons are indicated by minus signs. Contrast effect sizes are overlaid on axial cross sections. Images are displayed in radiological convention with the right hemisphere shown on the left. (Coronal and sagittal views are shown in Figure 4 and Figure 4—figure supplement 1; Figure 4—figure supplement 3 shows the magnitude of cluster differences.) Abbreviations: ALC$_M$ = alcoholic men; ALC$_W$ = alcoholic women; NC$_M$ = nonalcoholic men; NC$_W$ = nonalcoholic women.

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Figure 4—figure supplement 3. Contrast values observed in the cluster for erotic vs. neutral conditions. The split violin plot represents the Contrast Effect Size (CES, equivalent to ‘CON’ in SPM or ‘COPE’ in FSL) for the cluster in which a significant group x gender interaction was identified for the erotic vs. neutral contrast (p<0.05 after correction for multiple comparisons). Positive values indicate erotic >neutral, while negative values indicate erotic <neutral. Each point represents a single participant’s average CES for vertices within the cluster. This figure is meant to convey the variability in CES across participants that is not visible in Figure 4. Nonalcoholic control men had greater activation to erotic stimuli than neutral stimuli, and the contrast was more positive than was observed for alcoholic men. The pattern was reversed for women: Alcoholic women had lower contrast values than nonalcoholic women. Abbreviations: ALC = alcoholic participants; NC = nonalcoholic control participants.

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Figure 5. Aversive vs. neutral stimuli elicited more abnormally negative responses in alcoholic men. A significant group x gender interaction revealed several clusters (see Appendix 1—table 6), which are indicated by arrows on the lateral surface of the left hemisphere, overlaid on contrast values between aversive and neutral stimuli. Group mean contrast values (for aversive vs. neutral) are displayed in the four brain images located in the corners of the figure, and group comparisons are indicated by minus signs. (Figure 5—figure supplement 1 shows the medial surface, while the right hemisphere is shown in Figure 5—figure supplement 2 for the lateral and Figure 5—figure supplement 3 for the medial surface; Figure 5—figure supplement 4 shows the magnitude of cluster differences.) Although not shown here, the activation patterns across the four subgroups for contrasts of other emotional stimuli (i.e., happy, gruesome, and erotic) with neutral stimuli were similar to those shown above, and likewise, the general locations of the activation regions were similar for the four subgroups. Abbreviations: ALC\textsubscript{M} = Alcoholic men; ALC\textsubscript{W} = Alcoholic women; NC\textsubscript{M} = Nonalcoholic men; NC\textsubscript{W} = Nonalcoholic women.

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Figure 5—figure supplement 1. Aversive vs. neutral stimuli elicited more abnormally negative responses in alcoholic men (left medial surface). A group x gender interaction revealed several clusters (see Appendix 1—table 6), which are displayed as outlines and indicated by arrows on the medial surface of the left hemisphere, overlaid on contrast values between aversive and neutral stimuli. Group mean values (for aversive vs. neutral) are displayed in the four brain images located in the corners of the figure, and group comparisons are indicated by minus signs. (Figure 5 shows the lateral surface, while the right hemisphere is shown in Figure 5—figure supplement 2 for the lateral and Figure 5—figure supplement 3 for the medial surface; Figure 5—figure supplement 4 shows the magnitude of cluster differences.) Although not shown here, the activation patterns across the four subgroups for contrasts of other emotional stimuli (i.e., happy, gruesome, and erotic) with neutral stimuli were similar to those shown above, and likewise, the general locations of the activation regions were similar for the four subgroups. Abbreviations: ALC_M = alcoholic men; ALC_W = alcoholic women; NC_M = nonalcoholic men; NC_W = nonalcoholic women.

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Figure 5—figure supplement 2. Aversive vs. neutral stimuli elicited more abnormally negative responses in alcoholic men (right lateral surface). A group x gender interaction revealed several clusters (see Appendix 1—table 6), which are displayed as outlines and indicated by arrows on the lateral surface of the right hemisphere, overlaid on contrast values between aversive and neutral stimuli. Group mean values (for aversive vs. neutral) are displayed in the brain images located in the four corners of the figure, and group comparisons are indicated by minus signs. (Figure 5 and Figure 5—figure supplement 1 show the lateral and medial surfaces of the left hemisphere, while the medial surface of the right hemisphere is shown in Figure 5—figure supplement 3, Figure 5—figure supplement 4 shows the magnitude of cluster differences.) Although not shown here, the activation patterns across the four subgroups for contrasts of other emotional stimuli (i.e., happy, gruesome, and erotic) with neutral stimuli were similar to those shown above, and likewise, the general locations of the activation regions were similar for the four subgroups. Abbreviations: ALC_M = alcoholic men; ALC_W = alcoholic women; NC_M = nonalcoholic men; NC_W = nonalcoholic women.

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Figure 5—figure supplement 3. Aversive vs. neutral stimuli elicited more abnormally negative responses in alcoholic men (right medial surface). A group x gender interaction revealed several clusters (see Appendix 1—table 6), which are displayed as outlines and indicated by arrows on the medial surface of the right hemisphere, overlaid on contrast values between aversive and neutral stimuli. Group mean values (for aversive vs. neutral) are displayed in the brain images located in the four corners of the figure, and group comparisons are indicated by minus signs. (Figure 5 and Figure 5—figure supplement 1 show the lateral and medial surfaces of the left hemisphere, while the lateral surface of the right hemisphere is shown in Figure 5—figure supplement 2; Figure 5—figure supplement 4 shows the magnitude of cluster differences.) Although not shown here, the activation patterns across the four subgroups for contrasts of other emotional stimuli (i.e., happy, gruesome, and erotic) with neutral stimuli were similar to those shown above, and likewise, the general locations of the activation regions were similar for the four subgroups. Abbreviations: ALC\(_M\) = alcoholic men; ALC\(_W\) = alcoholic women; NC\(_M\) = nonalcoholic men; NC\(_W\) = nonalcoholic women.

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Figure 5—figure supplement 4. Contrast values observed in each cluster for aversive vs. neutral conditions. The split violin plot represents the Contrast Effect Size (CES; equivalent to ‘CON’ in SPM or ‘COPE’ in FSL) for left hemisphere clusters in which a significant group x gender interaction was identified for the aversive vs. neutral contrast (p<0.05 after correction for multiple comparisons). Positive values indicate aversive > neutral, while negative values indicate aversive < neutral. Each point represents a single participant’s average CES for vertices within the cluster. This figure is meant to convey the variability in CES across participants that is not visible in Figure 5. In each of the four clusters, nonalcoholic control men had greater activation to aversive stimuli than neutral stimuli, and the contrast was more positive than was observed for alcoholic men. The pattern was reversed for women: Alcoholic women had higher contrast values than nonalcoholic women. Abbreviations: ALC = alcoholic participants; NC = nonalcoholic participants.

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Figure 5—figure supplement 5. Aversive vs. neutral stimuli elicited more abnormally negative responses in alcoholic men (left lateral surface), cluster-forming threshold p<0.001. A group x gender interaction revealed two clusters (see Appendix 1—table 8), which are displayed as outlines and indicated by arrows on the lateral surface of the left hemisphere, overlaid on contrast values between aversive and neutral stimuli. Group mean values (for aversive vs. neutral) are displayed in the four brain images located in the corners of the figure, and group comparisons are indicated by minus signs. (The lateral surface of the right hemisphere is shown in Figure 5—figure supplement 6, no clusters were visible on medial surfaces).

Abbreviations: ALC<sub>M</sub> = alcoholic men; ALC<sub>W</sub> = alcoholic women; NC<sub>M</sub> = nonalcoholic men; NC<sub>W</sub> = nonalcoholic women.

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Figure 5—figure supplement 6. Aversive vs. neutral stimuli elicited more abnormally negative responses in alcoholic men (right lateral surface), cluster-forming threshold p<0.001. A group x gender interaction revealed two clusters (see Appendix 1—table 8), which are displayed as outlines and indicated by arrows on the lateral surface of the right hemisphere, overlaid on contrast values between aversive and neutral stimuli. Group mean values (for aversive vs. neutral) are displayed in the four brain images located in the corners of the figure, and group comparisons are indicated by minus signs. (The lateral surface of the left hemisphere is shown in Figure 5—figure supplement 5, no clusters were visible on medial surfaces).

Abbreviations: ALC<sub>M</sub> = alcoholic men; ALC<sub>W</sub> = alcoholic women; NC<sub>M</sub> = nonalcoholic men; NC<sub>W</sub> = nonalcoholic women.

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Figure 6. Interaction of group x gender for aversive, erotic, gruesome, and happy stimuli vs. neutral stimuli. Significant clusters are indicated by arrows shown on interaction maps of contrast values for each of the four emotions vs. neutral (similar to the center image in Figure 4 and Figure 5). All four brain surfaces are shown (from left: left lateral, left medial, right lateral, and right medial). Blue regions indicate less activation contrast (emotion vs. neutral) for ALC_M relative to NC_M vs. ALC_W relative to NC_W. Abbreviations: RH = Right Hemisphere; LH = Left Hemisphere.

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