

tinct brain regions. This knowledge, in turn, can offer important insights into intervention design. Neuroimaging can further provide information typically inaccessible via behavioral methods. Self-report may yield inaccurate responses, due to poor self-awareness (alexithymia) or biased responding, particularly when measuring socially undesirable traits and events. Participants may be reluctant to share embarrassing or guilt-evoking experiences or admit feelings of envy or schadenfreude. Some studies even suggest that the objective measurement of neural activity may better predict social behavior than subjective self-report.<sup>33</sup> Neuroimaging may also shed light onto modulators of social cognitive phenomena, such as reward-processing or in-group/out-group membership, which may lie outside conscious awareness.

## ASSOCIATED COGNITIVE PROCESSES AND THEIR NEURAL CORRELATES

### Moral cognition

The neural substrates of moral cognition have been studied in great detail.<sup>6,34</sup> Broadly, research converges on a fronto-temporo-subcortical network, including medial, lateral, and dorsolateral prefrontal cortex (mPFC, lPFC, dlPFC); anterior cingulate cortex (ACC); insula; anterior temporal lobe (aTL); posterior superior temporal sulcus (pSTS); precuneus (PC); amygdala; hypothalamus; and striatum.<sup>6</sup> This network represents context-dependent structured event knowledge, context-independent social perceptual and functional features, and motivational and affective states, respectively represented by prefrontal regions, anterior/posterior temporal regions, and a cortico-limbic network.<sup>6,35,36</sup>

### Empathy

An important process underlying both moral cognition and social emotion-processing is empathy. Decety described empathy as a functional bridge between first- and third-person information, enabling individuals to resonate with other people's affective states while distinguishing between self and other.<sup>37</sup> Empathy is supported by affect-sharing, perspective-taking, self-processing, and emotion regulation.<sup>37–39</sup> Recent meta-analyses highlight the primary roles of anterior insula and adjacent fronto-operculum (AI/FO; extending into inferior frontal

gyrus [IFG]) and ACC (particularly dorsal and middle regions [dACC/aMCC]).<sup>40,41</sup> AI supports interoceptive awareness,<sup>42</sup> uncertainty monitoring,<sup>1</sup> and salience-processing,<sup>43</sup> while ACC supports motivation-processing<sup>42</sup> and the integration of interoception and salience.<sup>44</sup> Some researchers advocate that AI and dACC/aMCC work together to represent and predict affective states, compute prediction errors, and guide social decision-making,<sup>38</sup> which support their roles in emotional inference and affective responding.

### Self-processing

Self-processing plays a significant role in moral cognition and social emotion-processing. Self-awareness and self-reflection are necessary for representing personal agency and for monitoring, evaluating, and regulating social behavior. Self-other decoupling is critical for distinguishing between one's own cognitive and affective states and those of another person, in order to empathize with others while avoiding personal distress. Furthermore, self-other decoupling is necessary for social comparison, and self-relevance modulates feelings of envy and schadenfreude.<sup>26</sup> Self-processing primarily recruits cortical midline structures, including mPFC (dorsal, anterior rostral, and ventral regions [dmPFC, armPFC, vmPFC], and ACC) and medial posterior parietal cortex (mPPC; PC, posterior cingulate cortex [PCC], and retrosplenial cortex [RSC]).<sup>45–48</sup>

### Theory of mind

Perspective-taking, or theory of mind (ToM) is another important component. During SCE-processing, a person infers how his/her social behaviors are evaluated by others, and during FOE-processing, a person attributes others' affective reactions to their fortunes/misfortunes. ToM is supported by a distinct fronto-temporo-parietal network, consisting of mPFC, pSTS, temporo-parietal junction (TPJ), temporal poles (TP), and PC/PCC.<sup>48,49</sup> Broadly, social emotion-processing recruits superior frontal gyrus (SFG), TP, and PC/PCC, underscoring the importance of mental state attribution.<sup>48</sup> Research suggests that TP represents social emotional, third-person perspective-taking;<sup>48</sup> right TPJ tracks intention attribution during moral cognition;<sup>50</sup> and mPFC, PCC, and inferior parietal lobe (IPL) support emotional salience-processing during moral decision-making.<sup>51</sup>

## Reward-processing

Reward-processing is highly relevant to envy and schadenfreude. Both primary and secondary reward-processing recruits mesolimbic regions, in particular dorsal striatum (DS; caudate, putamen) and ventral striatum (VS, including nucleus accumbens [NAcc]). In addition, a prefronto-striatal network is often recruited when processing losses and gains.<sup>52–55</sup> Social preferences and rewarding social behaviors, such as cooperation, punishment, and charitable giving, are also affiliated with striatal activity.<sup>56,57</sup> This suggests that envy may represent diminished reward-processing and reduced striatal recruitment, while schadenfreude may represent heightened reward-processing and increased striatal recruitment.

While the general neural circuitry underlying social emotions and associated cognitive processes has been examined extensively, the investigation of *distinct* social emotions is currently in its nascence. Moll *et al.* suggested that social emotions are supported by a partially dissociable prefronto-temporo-limbic system.<sup>6</sup> Below, we review recent neuroimaging research exploring embarrassment, guilt, envy, and schadenfreude, and discuss important clinical implications.

## NEURAL BASIS OF EMBARRASSMENT

Elucidating the neural correlates of embarrassment is highly relevant towards better understanding clinical symptomatology. A host of psychological disorders are characterized by socially inappropriate behaviors, which can negatively affect interpersonal relationships and impair adaptive functioning. In particular, patients with mPFC damage (e.g., vmPFC lesions/orbital frontal cortex [OFC] lesions, frontal temporal lobe degeneration [FTLD]) or mPFC dysfunction (e.g., autism spectrum disorders [ASD], schizophrenia) demonstrate a diminished understanding of embarrassment, commonly attributed to impaired ToM.<sup>58–61</sup>

Faux pas tasks shed light onto atypical processes underlying impaired embarrassment-processing within clinical populations. Patients with OFC lesions, relative to lateral frontal, dorsal frontal, or non-frontal lesions, or typically developing controls, demonstrate poor faux pas recognition, particularly when making inferences about transgressors' intentions, yet intact first-order ToM, second-order ToM,

and empathic understanding.<sup>60,62</sup> These results demonstrate that OFC damage may not impair cognitive perspective-taking or empathy, per se, but the *integration* of mental state attribution with empathic understanding and emotion-processing. The authors posited that similar social cognitive deficits observed in mPFC damage and ASD may represent common vmPFC/OFC impairment.<sup>62,63</sup>

Beer *et al.* were particularly interested in the impact of mPFC damage on social regulation and SCE recognition.<sup>64,65</sup> OFC patients, LPFC patients, and typically developing controls completed tasks assessing self-disclosure, teasing, over-praise, and emotion recognition. OFC patients provided appropriate definitions of basic and self-conscious emotions, yet revealed impaired recognition of SCE facial expressions and displayed inappropriately intimate self-disclosures and teasing. OFC patients failed to demonstrate socially appropriate embarrassment and reparative actions following social transgressions, yet displayed socially inappropriate embarrassment when it was unwarranted. In general, OFC patients underestimated the inappropriateness of their own behaviors, but demonstrated heightened embarrassment following increased self-monitoring. These findings suggest that OFC patients have intact conceptual social knowledge but fail to apply this information to infer others' emotions or guide social decisions. Consequently, OFC patients display socially inappropriate behaviors, including atypical embarrassment, which may represent altered self- and other-awareness.

FTLD is similarly associated with atypical embarrassment-processing. In response to an acoustic startle response task, FTLD patients demonstrated intact physiological and basic emotional responding, but impaired SCE responding (diminished embarrassment facial expressions).<sup>66</sup> Prefrontal, temporal, and subcortical gray matter volume was negatively correlated with physiological and emotional responding to embarrassing situations, and right perigenual ACC volume was a significant predictor of physiological and emotional embarrassment responding.<sup>67</sup> These findings highlight the importance of PFC/vmPFC in self-monitoring and emotional perspective-taking, which are necessary for processing embarrassment. The authors suggested that socially inappropriate behaviors observed in mPFC damage, including diminished embarrassment expression, reduced embarrassment recognition, increased social norm violations, and decreased

reparative actions, may represent impaired self-awareness and poor affective ToM.

Atypical embarrassment is also observed in ASD, neurodevelopmental disorders characterized by social and communicative deficits, restricted interests, and repetitive behaviors.<sup>68</sup> People with ASD demonstrate impaired social cognition, including atypical self-processing, complex cognitive and affective ToM, and empathy,<sup>69–72</sup> as well as altered underlying neural circuitry, including mPFC, ACC, AI, IFG, TPJ/pSTS, PC/PCC, and amygdala.<sup>59,73–78</sup> Performance on moral reasoning tasks demonstrates the impact of impaired affective perspective-taking on social decision-making. When evaluating moral behavior, people with ASD often give more weight to outcomes than intentions, rating accidental and attempted harms as equally unacceptable,<sup>79</sup> and rating agents of accidental harms as more responsible and more deserving of punishment than typically developing controls.<sup>80</sup> Buon *et al.* suggested that atypical moral reasoning in ASD may represent misattribution of intentions and elevated severity of moral evaluation.<sup>80</sup>

Similar to mPFC patients, people with ASD demonstrate impaired performance on faux pas tasks, including poor differentiation between sad and embarrassing situations, less frequent and explicit reference to an audience, impoverished justifications, and atypical severity ratings.<sup>63,81–84</sup> When asked to identify the content of transgressions, people with ASD more frequently referenced rule violations or poor manners, but rarely referenced another person's welfare.<sup>79</sup> Furthermore, atypical severity ratings of norm violations were associated with impaired cognitive ToM (but not empathy).<sup>83,84</sup> These findings offer additional evidence that people with ASD over-emphasize external outcomes and deemphasize mental states (intentions) during moral reasoning and embarrassment-processing. Thus, ASD may be associated with intact conceptual social knowledge and false belief-processing, but a diminished ability to integrate social rules and mental states in everyday social interactions, particularly when mental state information conflicts with outcome information.<sup>79,85</sup> Overall, this research suggests that ASD are associated with atypical embarrassment-processing, due to impaired mental state representation and evaluation, possibly indicating altered ToM neural circuitry.

Findings from neuroimaging research converge with those from clinical studies, underscoring the importance of prefrontal and temporal regions in

mental state attribution. Berthoz *et al.* investigated the neural correlates of unintentional (embarrassing) and intentional social norm violations in typically developing adults.<sup>86,87</sup> Unintentional transgressions recruited bilateral prefrontal (right medial and superior PFC, left middle and inferior PFC, left OFC), bilateral temporal (bilateral anterior and middle TP, left TPJ), and occipital regions. While unintentional and intentional violations similarly recruited bilateral prefrontal (left medial, middle, and inferior PFC, left OFC, bilateral SFG), bilateral temporal (bilateral anterior and middle TP, left TPJ), and occipital regions, unintentional violations recruited greater left TP. Thus, processing social norm violations (regardless of intentionality) requires ToM (mPFC, temporal regions) and negative emotion-processing (lPFC, mPFC), which likely aids in inferring transgressors' intentions, observers' evaluations, and observers' emotional reactions. Furthermore, greater TP recruitment during unintentional, relative to intentional, violations likely represents enhanced emotional perspective-taking and affective empathy.<sup>48,88,89</sup>

Takahashi *et al.* similarly highlighted the roles of mPFC and temporal regions in embarrassment-processing.<sup>90</sup> Participants read sentences representing first-person embarrassment (e.g., 'I noticed that the zipper on my pants was open'), guilt (e.g., 'I shoplifted a dress from the store'), and neutral emotion, and rated emotional intensity. Embarrassment recruited bilateral prefrontal (bilateral mPFC, left OFC), bilateral temporal (left pSTS, bilateral ATL, left middle temporal, left hippocampal), and occipital regions, and left pSTS and right occipital activity was positively correlated with embarrassment intensity. These neural patterns underscore the importance of perspective-taking (mPFC), social perception (pSTS), memory (hippocampus), and attention/salience (occipital cortex) in embarrassment-processing. They also converge with reports of greater frontal (MFG, ACC), insula/IFG, and superior temporal/inferior parietal (STS/TPJ, IPL/TPJ) recruitment during embarrassment-processing, relative to neural agency.<sup>91</sup> Furthermore, compared to guilt, embarrassment recruited greater right ATL, bilateral hippocampus, and bilateral occipital regions. The authors posited that greater temporal and occipital recruitment during embarrassment represented greater complexity (requiring greater discernment of social conventions).

A German replication study reported similar results.<sup>92</sup> Embarrassment recruited bilateral frontal

(SFG, IFG), bilateral temporal (left superior temporal gyrus [STG], bilateral parahippocampus), and occipital regions. Embarrassment and guilt commonly recruited prefrontal, temporal, and occipital regions, but embarrassment, relative to guilt, recruited greater right frontal (MFG, ACC) and bilateral temporal (parahippocampus) regions.

Overall, these studies suggest that embarrassment recruits a network of frontal (mPFC/OFC), temporal (pSTS, anterior and middle temporal cortex) and occipital regions, representing self-processing, mental state attribution, social semantic-processing, and emotional salience. Relative to guilt and intentional norm violations, embarrassment recruits greater ATL, representing greater conceptual social knowledge and richness of social detail.<sup>35,36</sup> This highlights the importance of identifying and understanding culturally dependent social norms during embarrassment-processing and distinguishing between socially appropriate and inappropriate behaviors.

## NEURAL BASIS OF GUILT

Guilt-processing plays a significant role in the development and maintenance of psychopathology, including depression, anxiety, obsessive–compulsive disorder (OCD), and somatization.<sup>93</sup> In particular, impaired moral cognition and guilt are characteristic of antisocial personality disorder (APD) and psychopathy, likely representing intact ToM but impaired affective-processing.<sup>94</sup> Gray matter reductions within prefrontal (mPFC, medial/lateral OFC), AI, and temporal (STS, ATL) regions are associated with conduct disorder,<sup>95</sup> APD,<sup>96</sup> interpersonal/affective psychopathic traits,<sup>97</sup> and callous and unemotional traits.<sup>95</sup> Psychopathy is associated with a range of social cognitive and emotional deficits, representing underlying cortico–subcortical dysfunction. Violent psychopaths demonstrate decreased metabolism within prefrontal, parietal, and limbic regions,<sup>98</sup> and prisoners high in psychopathy show reduced AI and ACC activity during empathy-processing.<sup>99</sup>

A related set of studies has investigated the impact of adult-onset vmPFC/OFC damage on ‘acquired psychopathy’.<sup>100–102</sup> A famous case study of Patient JS demonstrated that OFC damage is associated with intact ToM and social norm knowledge, but impaired emotion recognition, affective responding, emotional reaction prediction, and moral judgment.<sup>101</sup> A larger sample of patients with adult-onset vmPFC

damage revealed typical responding to *impersonal* moral dilemmas but enhanced utilitarian responding to highly *emotional, personal* moral dilemmas.<sup>103</sup> Blair *et al.* posited that diminished guilt, reduced empathy, atypical emotional responding and antisocial behavior may represent underlying OFC–amygdala dysfunction, which impairs the prediction of negative emotional reactions.<sup>101,104</sup> These studies shed light onto the possible neural mechanisms of guilt-processing by highlighting the importance of prefrontal regions, particularly OFC, in the generation and application of emotional expectations, which guide social decision-making.

A large body of neuroimaging research has explored guilt-processing within typical development. One of the earliest studies used positron emission tomography to examine guilt recollection.<sup>105</sup> Participants listened to audio-recordings of guilt-evoking or neutral autobiographical events and used script-driven imagery to recall them. Guilt recruited empathy regions highly connected with amygdala,<sup>106</sup> including left AI/IFG, ACC, and bilateral ATL. Despite using stimuli that evoked multiple negative emotions, this study offers preliminary evidence for anterior paralimbic recruitment during guilt-processing, possibly representing negative emotional responding.

A related autobiographical memory study extended these findings by comparing the neural correlates of multiple negative emotions.<sup>107</sup> Guilt, shame, and sadness commonly recruited regions supporting ToM, empathy, self- and other-processing, and emotional memory retrieval, including bilateral medial frontal pole, left AI, bilateral RSC (extending into PC/PCC), bilateral TP, left TPJ, left aSTS, bilateral lingual gyrus, and cerebellum. Guilt, relative to shame, recruited greater right dlPFC/anterior SFG and right amygdala (also recruited during other-processing). Guilt, relative to shame and sadness, recruited greater right lateral OFC (lOFC) and left paracingulate/dmPFC (also recruited during self-processing), and lOFC activity was positively correlated with dispositional guilt. These findings support the role of self-reference and ToM in guilt-processing, and suggest that perspective-taking demands are greater for guilt-processing than shame or sadness. Furthermore, the authors posited that lOFC activity represented inhibition of social norm violations or anticipation of negative outcomes, and proposed a dissociation within PFC, such that vmPFC represented general social emotion-processing, while OFC

uniquely represented guilt-processing. Thus, IOFC activity may not simply represent negative valence or SCE, but instead, serve as a distinct marker for transient guilt-processing and guilt sensitivity.

Multiple studies have highlighted the role of prefrontal, temporal, and occipital regions during imagined guilt-processing. Takahashi *et al.* reported bilateral mPFC, left pSTS, and bilateral occipital recruitment during imagined guilt-evoking situations, and greater left mPFC recruitment, relative to embarrassment.<sup>90</sup> A German replication reported similar frontal, temporal, and limbic recruitment, including bilateral PFC, left OFC, left precentral gyrus, left insula, bilateral temporal (middle temporal gyrus [MTG], STG), and bilateral occipital regions.<sup>92</sup> Guilt recruited greater right amygdala/insula, left MTG, and right fusiform gyrus, relative to embarrassment, possibly underscoring the greater role of negative emotion-processing.<sup>108,109</sup> Berthoz *et al.* similarly reported bilateral PFC, left TPJ, bilateral ATL, and occipital recruitment during intentional violations (guilt). Intentional, relative to unintentional, violations recruited greater left PFC (mPFC, superior PFC, ACC), precentral/postcentral gyri, right TP, left IPL, PC, and occipital regions,<sup>86</sup> which the authors suggested represented greater mentalizing demands required to infer the motivations, and thus liability, of intentional transgressors. Personal, intentional violations recruited greatest bilateral amygdala.<sup>87</sup>

Recent neuroimaging studies have begun to investigate cognitive and motivational modulators of guilt-processing, including agency, social consequence, behavioral change demands, and guilt-sensitivity/aversion. Moll *et al.* investigated the neural correlates of emotionally neutral agency and moral emotions.<sup>91</sup> Neutral agency recruited prefrontal, insular, and anterior/superior temporal regions, associated with ToM, empathy, self-reference, and conceptual social knowledge, and guilt recruited greater right anterior PFC (MFG, IOFC), left insula, right midbrain (ventral tegmental area [VTA], thalamus), and left anterior/superior temporal regions (STS/TPJ). Conjunction analyses revealed unique neural patterns for distinct emotion categories: prosocial emotions (guilt, embarrassment, compassion) recruited anterior mPFC and STS/TPJ; empathic emotions (guilt, compassion) recruited VTA and VS; and other-critical emotions (self-indignation, other-indignation, disgust) recruited dACC, IOFC, and parahippocampus/amygdala. Relative to other-critical emotions, prosocial emotions recruited

greater medial OFC (mOFC) and TP, and empathic emotions recruited greater anterior PFC, VTA, and VS. These findings emphasize the importance of anterior PFC, midbrain, and temporal regions in guilt-processing, supporting prosociality and empathy.

Morey *et al.* examined the impact of social consequences in guilt-processing.<sup>110</sup> Imagining harming others, compared to harming oneself, was associated with greater right mPFC (vmPFC, dorsomedial PFC [dmPFC] frontal pole [FP]), bilateral pSTS, bilateral PC/PCC, and right occipital recruitment. Guilt-sensitivity was positively correlated with left PFC (dmPFC, SFG, OFC, ventrolateral PFC [vlPFC], paracingulate gyrus; subgenual ACC/septal area [SCSR] at a reduced threshold) and supramarginal gyrus activity. Furthermore, an interaction between guilt intensity and social consequence within left vmPFC/FP, OFC, IFG, and anterior IPL suggested that anterior frontal and parietal activity tracks guilt-sensitivity associated with harming others.

A strong motivator for behavior modification and reparation is fear of negative evaluation. Finger *et al.* examined how the presence of an audience impacted guilt-processing.<sup>111</sup> Moral violations, which elicited highest guilt ratings, recruited greater left dmPFC and bilateral temporal regions (TP, middle temporal gyrus [MTG]) than social violations. Regardless of an audience presence, moral and social violations recruited left TPJ, underscoring shared perspective-taking demands; however, moral and *witnessed* social violations commonly recruited left vlPFC and dmPFC, which the authors interpreted as representing behavioral change demands.

A final set of studies has examined guilt-proneness and associated neural modulators. Using a donation task, Chang *et al.* found that guilt-aversion and guilt-sensitivity were associated with dlPFC, as well as dACC, insula, supplementary motor area (SMA), and TPJ activity, which was positively correlated with counterfactual guilt.<sup>112</sup> In a study by Zahn *et al.*, participants read sentences evoking guilt, indignation, pride, and gratitude.<sup>113</sup> Guilt-proneness was positively correlated with bilateral prefrontal (left anterior vmPFC, left subgenual ACC [sgACC], bilateral ventral ACC) activity. A subsequent psychophysiological interaction (PPI) analysis revealed functional connectivity between right superior ATL (sATL) and bilateral sgACC during guilt-processing, which was positively correlated with guilt-proneness.<sup>114</sup> Other research suggested that sgACC activity during guilt-processing was positively correlated with indi-

vidual differences in empathic concern.<sup>115</sup> These neural patterns highlight functional integration between right sATL, representing conceptual social knowledge, and context-dependent fronto–limbic regions, representing distinct moral emotions. In particular, sgACC activity may serve as a distinct neural marker for guilt-proneness, supported by dispositional empathy.

These findings have important implications for understanding and treating major depressive disorder (MDD). Patients with MDD demonstrate excessive or inappropriate guilt associated with heightened self-blame.<sup>116</sup> Research investigating guilt-proneness in MDD revealed intact ATL and SCSR recruitment, but reduced functional coupling between right sATL and left SCSR, as well as between bilateral medial frontal pole, right hippocampus, and right lateral hypothalamus.<sup>117</sup> Furthermore, sATL–SCSR decoupling was positively correlated with self-hate ratings. The authors suggested that this decoupling represented reduced integration of conceptual social knowledge,<sup>35</sup> specific memories, and guilt-processing,<sup>114</sup> resulting in overgeneralized self-blame, and thus, elevated guilt-proneness. Preliminary research suggests that SCSR deep brain stimulation may effectively treat abnormal guilt-processing in MDD.<sup>118</sup>

Neuroimaging research investigating guilt also sheds light onto OCD etiology. Clinical studies suggest that OCD is associated with atypical guilt-processing, driven by inner moral rule violations.<sup>119,120</sup> Research by Basile *et al.* found that OCD patients recruited a typical prefronto–temporo–occipital network when processing anger and sadness, but reduced ACC, bilateral AI and left PC recruitment during guilt-processing, which was negatively correlated with OCD symptoms.<sup>121</sup> These findings demonstrate intact basic negative emotion-processing in OCD, but impaired (possibly overly efficient<sup>122</sup>) guilt-processing, elicited by personal moral transgressions.

These studies suggest that guilt-processing recruits a network of anterior prefrontal (vmPFC, mOFC/IOFC, sgACC), fronto–opercular (AI/IFG), temporal (ATL, TP, STS, TPJ), medial posterior parietal (PC, RSC), limbic (amygdala), and occipital (including fusiform gyrus) regions supporting perspective-taking, empathy, self-processing, other-processing, and negative emotion-processing. In particular, IOFC–amygdala and sATL–SCSR coupling may support guilt-proneness. Relative to other negative

emotions, such as embarrassment, shame, and sadness, guilt recruits greater PFC (mPFC, dmPFC, dlPFC, OFC, ACC), amygdala, and ToM regions (TP, pSTS, IPL, PC). Furthermore, neuroimaging findings help dissociate the cognitive and emotional modulators of guilt-processing: social agency recruits a prefronto–insular–superior temporal network, associated with moral cognition; empathic motivation recruits VTA and VS, associated with social attachment; negative emotional prediction and responding recruits IOFC and parahippocampus/amygdala; prosocial motivation recruits anterior mPFC and STS; and behavioral change demands/compensatory behavior recruits vlPFC and dmPFC.

### NEURAL BASIS OF ENVY AND SCHADENFREUDE

A large body of research has examined the neural correlates of social comparison and its relation to prosocial and antisocial behaviors. Typically, these studies have either adopted a neuroeconomics approach, where participants made monetary allocation decisions or competed against a confederate for monetary rewards, or a social psychological approach, where participants made costly helping decisions or compared themselves with others along highly self-relevant domains. In general, these studies underscore the importance of a prefronto–striatal network, particularly VS, for processing envy and schadenfreude. Critical work by Fleissbach *et al.* investigated the neural correlates of relative reward-processing.<sup>123</sup> Participants competed against a partner in a dot estimation task and received monetary rewards for correct answers. A main effect of inequality was found within OFC and posterior regions (angular gyrus, PC/PCC, occipital), such that larger reward discrepancies between the partners were associated with greater activity. A main effect of relative reward was found within bilateral VS, such that relatively larger rewards recruited greater VS activity, equal rewards recruited intermediate activity, and relatively smaller rewards recruited reduced activity, independent of absolute rewards. This VS response was positively correlated with willingness to reciprocate, such that greater concern for relative outcomes was associated with a greater tendency to reciprocate prosocial and antisocial behaviors. Related electroencephalography (EEG) studies revealed similar neural patterns; relative outcomes recruited prefrontal (mPFC/ACC),

striatal, and parahippocampal activity, possibly supporting perspective-taking, monitoring, and reward-processing, and unequal gains were rated more positively and recruited greater mPFC and caudate activity than equal gains.<sup>124,125</sup>

Research exploring inequality aversion extended these findings.<sup>126</sup> Pairs of participants played a monetary allocation task after economic inequality was manipulated (one participant received a large monetary endowment ['rich'], the other did not ['poor']). 'Rich' participants rated transfers to others (advantageous inequality aversion) positively and recruited increased frontal and striatal activity. 'Poor' participants rated transfers to others negatively and recruited reduced frontal and striatal activity, even though these transfers did not influence their own financial status (envy); however, they rated transfers to themselves (disadvantageous inequality aversion) positively and recruited increased activity. These findings offer further support that inequality-averse social preferences modulate vmPFC and VS recruitment during relative losses and gains.

Research comparing the neural correlates of absolute and relative losses and gains offer additional evidence for a prefronto–striatal network underlying envy and schadenfreude. Using a game of chance, Dvash *et al.* found that relative losses evoked greater envy but recruited similar VS activity as absolute losses, while relative gains evoked greater schadenfreude but recruited similar VS activity as absolute gains.<sup>127</sup> Thus, relative losses and gains were processed similarly to absolute losses and gains on the neural level. Research exploring private (absolute) and public (relative) lottery outcomes revealed similar neural patterns.<sup>128</sup> Results revealed a main effect of outcome valence within OFC and DS; a main effect of outcome context within PFC (mPFC, dlPFC), VS, and TPJ; and an interaction effect between outcome valence and context within DS. Participants recruited greater caudate during relative gains compared to absolute gains, and reduced caudate and NAcc during relative losses compared to absolute losses. These results highlight the impact of social context on the subjective value, affective experience, and neural basis of reward-processing.

Research examining the modulatory role of learned preferences in empathy and counterempathy offer additional support for an underlying fronto–striatal network. In a seminal study by Singer *et al.*, participants observed confederates play fairly or unfairly during a neuroeconomic game and receive painful

stimulation. Both male and female participants recruited empathy-related AI/FO and ACC activity when they observed fair players in pain, which was positively correlated with self-reported empathy.<sup>129</sup> However, male participants recruited reduced empathy-related AI/FO activity and increased reward-related VS activity when they observed unfair players in pain, which was respectively correlated with diminished empathy and an enhanced desire for revenge.

Similar neural patterns were found in studies where participants observed out-group members in pain. In a study capitalizing on a real-world sports rivalry, Yankees and Red Socks fans watched clips of a computer-generated baseball game.<sup>33</sup> During absolute and relative losses (favorite team lost or rival team won), participants recruited right sensorimotor (insula, ACC, SMA) regions. During absolute and relative gains (favorite team won or rival team lost), participants recruited left frontal (MFG, SFG), bilateral striatal (right VS, bilateral DS), and bilateral sensorimotor (left insula, right SMA) regions, and this VS response was positively correlated with self-reported pleasure and likelihood of harming a rival fan. This suggests that absolute and relative gains are similarly rewarding on a subjective and neural level, and VS activity associated with schadenfreude predicts antisocial behavior. In a related study, local soccer players recruited reduced empathy-related left AI and increased reward-related right NAcc activity when they observed rival players in pain.<sup>130</sup> Furthermore, negative impressions of rivals predicted greater AI reduction and NAcc recruitment, and both negative impressions and NAcc recruitment predicted costly helping behavior (volunteering to experience pain on behalf of another player).

Research has also examined neural modulators of social cooperation and competition. When observing racial out-group members in pain, participants demonstrated diminished empathic responding, including reduced ACC, SMA, and insula recruitment.<sup>131</sup> Research also suggests that stereotypes of warmth and competence influence empathy/counterempathy, beyond the effect of out-group membership.<sup>132,133</sup> When envied targets experienced negative events, participants felt greatest pleasure, yet when envied targets experienced positive events, participants felt greatest displeasure, which was associated with increased right insula/MFG and superior parietal recruitment. Furthermore, bilateral insula activity during positive events was positively correlated with



willingness to harm envied targets, but negatively correlated with willingness to harm pride targets. Overall, these findings suggest that a fronto–sensorimotor–striatal network supports empathy and counterempathy for pain and predicts prosocial and antisocial behaviors.

Several studies have investigated envy and schadenfreude via social comparison of self-relevant traits. Takahashi *et al.* reported fronto–striatal recruitment, including mOFC, dACC, VS, and DS, when participants compared themselves to superior targets.<sup>134</sup> dACC activity was positively correlated with envy, striatal activity was positively correlated with schadenfreude, and envy-related dACC activity predicted schadenfreude-related VS activity. The authors suggested that dACC activity represented distress resulting from self-concept threat (similar to cognitive dissonance<sup>135</sup>) or social pain resulting from salient upward social comparison (similar to social exclusion<sup>136</sup>), which motivates cognitive dissonance reduction via attitudinal change or schadenfreude. The authors interpreted the results to suggest that greater pain during self-concept threat (greater envy-related dACC activity during upward social comparison) was associated with greater reward during cognitive dissonance reduction (greater schadenfreude-related VS activity during others' misfortunes).

Friederich *et al.* investigated a highly salient domain of social comparison, body shape, in female adults.<sup>137</sup> Participants recruited bilateral frontal (left ACC, right dlPFC/precentral gyrus), right inferior parietal, and bilateral occipitotemporal regions when comparing their own bodies to images of slim, idealized figures, converging with ACC recruitment reported during envy-processing. Anxiety during body shape comparison was positively correlated with body concerns, disordered eating, and ventral limbic recruitment, including dACC, vlPFC, basal ganglia, amygdala, and occipital regions. The authors suggested that these neural patterns supported fear-processing, motivation, and emotion-processing, and represented body dissatisfaction and risk of eating disorders.

A follow-up study explored social comparison in anorexia as a means of understanding body dissatisfaction.<sup>138</sup> During body shape comparison, patients with anorexia recruited right lPFC, right PC, left superior parietal, and bilateral occipitotemporal regions. Relative to controls, patients reported greater body dissatisfaction and recruited reduced left rostral ACC

and increased right sensorimotor (AI, including putamen and premotor) activity, which was negatively correlated with anorexia symptoms. These results suggest that body dissatisfaction in anorexia does not represent atypical envy-processing, as demonstrated by intact ventral limbic activity, but instead, likely represents altered self-processing/interoception and motivation/emotion-processing, as demonstrated by atypical sensorimotor activity. Interventions designed to improve body satisfaction in anorexia should address distorted self-perceptions and unhealthy motivations.

A final set of studies has investigated atypical envy- and schadenfreude-processing associated with prefrontal dysfunction. Shamay-Tsoory *et al.* examined FOE recognition and ToM abilities in lesion patients using an eye gaze task.<sup>139</sup> Patients with both vmPFC and dlPFC lesions demonstrated impaired cognitive and affective ToM; patients with vmPFC lesions or both vmPFC and dlPFC lesions demonstrated impaired envy recognition; and patients with vmPFC lesions, both vmPFC and dlPFC lesions, or inferior parietal/temporo-parietal lesions demonstrated impaired schadenfreude recognition. Furthermore, envy and schadenfreude recognition were associated with real-world perspective-taking. These findings underscore the importance of complex mental state attribution in FOE-processing. In particular, vmPFC is important for processing envy, while both vmPFC and inferior parietal/temporo-parietal regions are important for processing schadenfreude. A follow-up study examined FOE-processing in adults with ASD.<sup>140</sup> Participants with ASD demonstrated intact 1st- and 2nd-order ToM, but impaired real-world perspective-taking and diminished envy and schadenfreude recognition. These findings lend further support for the role of complex mental state attribution in FOE, and suggest that impaired envy- and schadenfreude-processing in ASD may represent underlying ToM deficits.

Overall, these studies offer evidence for a prefronto–striatal network underlying envy and schadenfreude and highlight a neural basis for the modulatory roles of target superiority and trait self-relevance. In particular, research underscores the roles of vmPFC and inferior parietal/temporo-parietal regions in perspective-taking and self-relevance; striatal regions (especially VS) in reward-processing; and a ventral limbic network in fear-processing, emotion-processing, and motivation. Research further highlights the influence of



social context on reward-processing. Similar to absolute losses, relative losses (envy) are associated with increased dACC activity, representing cognitive dissonance, and decreased striatal activity, representing diminished subjective value and reward. Similar to absolute gains, relative gains (schadenfreude) are associated with reduced insular activity, representing diminished empathy, and increased striatal activity, representing enhanced subjective value and reward. Finally, neural recruitment during social comparison significantly predicts prosocial (costly helping) and antisocial (physically harming) behaviors.

## FUTURE DIRECTIONS

The current literature provides a strong foundation for elucidating the neural patterns of distinct social emotions, as well as for shedding light onto neural dysfunction underlying psychopathology. The neurobiology of social emotions is a burgeoning field with several lines of research ripe for investigation. In the following sections, we discuss ongoing questions, suggest topics for future research, and describe potential treatment avenues.

### Ecologically valid paradigms

This review has summarized popular paradigms for investigating social emotions, while highlighting prime areas for further development. Since this research is still in its nascence, previous studies have generally implemented strictly controlled designs with straightforward manipulations. Future studies should adopt more ecologically valid paradigms, using stimuli that more closely resemble variables of interest.

Research investigating SCE has commonly used vignettes, encouraging participants to imagine emotion-eliciting situations or rate the severity of hypothetical transgressions. While these tasks use prototypical examples of social emotions, they often lack personal relevance and emotional salience, characteristics that drive the experience of these emotions in the real world. Future studies should use more realistic, interactive stimuli, such as dynamic videos, or elicit emotions online. Research would benefit from adopting a combined approach of evoking emotions in real-time, tracking subjective ratings of emotional intensity, and measuring self-reported emotional tendencies and real-world behaviors.

Research examining FOE has typically adopted neuroeconomics paradigms, tracking donation behavior or measuring responses to monetary losses and gains. These tasks afford the development of computational models that further the understanding of social cooperation and competition. However, these tasks serve as abstract proxies for FOE, and may not accurately reflect real-world decision-making. Future research should elicit social comparisons online, along highly self-relevant domains, relative to salient, familiar social targets. A popular paradigm for studying schadenfreude has assessed empathic/counterempathic reactions when participants observe rivals in physical pain. Future studies should extend this research to examine empathic/counterempathic responses to more realistic, non-physical misfortunes.

### Developmental and clinical samples

Previous research has primarily examined typically developing adults, yet few studies have explored developmental trends. Adolescence is a stage of significant growth, characterized by enhanced self-awareness, perspective-taking, and social comparison, as well as neural maturation of the 'social brain'.<sup>141–144</sup> Adolescence is an ideal developmental period for investigating changes in social emotion-processing. In addition, preliminary research suggests that SCE-processing may continue to develop into late adulthood.<sup>145</sup> Future studies should investigate the neurodevelopmental trajectories of social emotion-processing from pre-pubescence, through adolescence, and into adulthood.

Research should also more extensively explore differences in social emotion-processing within psychopathology. Embarrassment has largely been studied within the context of prefrontal damage, yet minimally within neuropsychiatric disorders, and envy and schadenfreude have rarely been investigated outside of typical development. Future studies should examine a wider range of clinical populations, particularly patients characterized by diminished perspective-taking abilities, atypical self-awareness, and altered reward-processing. Additionally, findings from typical development should be applied towards clarifying the etiology of clinical symptoms, as demonstrated by Friederich *et al.*,<sup>137,138</sup> as well as towards exploring compensatory mechanisms adopted in response to social cognitive impairments.

### Avenues for treatment/intervention

Investigating the neural correlates of social emotions has significant implications for designing clinical interventions. First, researchers can determine the impact of specific cognitive deficits on social emotion-processing and design interventions to increase these abilities. For example, Beer *et al.*<sup>64</sup> demonstrated that atypical embarrassment in patients with PFC damage might reflect diminished self-awareness, and increased self-monitoring via video observation may improve embarrassment recognition. Future cognitive interventions may aim to increase self-monitoring, perspective-taking, or interoception.

Second, neuroendocrine interventions may enhance social emotion-processing and reduce associated clinical impairments. In particular, a subcortical neuropeptide called oxytocin significantly influences broad social behavior, including social bonding,<sup>146,147</sup> empathy,<sup>148,149</sup> and social salience,<sup>150–152</sup> as well as FOE.<sup>153,154</sup> Oxytocin administration modulates cooperation and competition among in-group and out-group members, empathic responding to others' pain, and associated neural recruitment, including prefrontal, inferior parietal/temporo-parietal, and striatal activity.<sup>153</sup> Of particular relevance, oxytocin administration increases envy and schadenfreude when participants process relative losses and gains.<sup>154</sup> These findings suggest that oxytocin may effectively increase the saliency of social emotion-processing. Future research should examine the impact of oxytocin on a range of social emotions.

Research has also highlighted the role of oxytocin in the manifestation of clinical symptoms. A popular line of research has explored the impact of oxytocin administration on reducing ASD symptoms, revealing decreased repetitive behaviors,<sup>155</sup> enhanced emotion recognition,<sup>156</sup> and increased social salience.<sup>157</sup> Future research should examine the impact of oxytocin on social emotion-processing across multiple clinical disorders, such as schizophrenia or MDD.

A third line of research has examined the efficacy of real-time functional magnetic resonance imaging (fMRI) to measure and modulate brain activity.<sup>158</sup> EEG neurofeedback and transcranial magnetic stimulation have reduced spatial resolution, which limits these methods to only measuring cortical activity; however, real-time fMRI affords the measurement of subcortical activity, such as striatal and limbic

regions, which is integral for investigating social emotion-processing. During real-time fMRI, participants complete tasks in the MRI scanner while neural activity from regions of interest are simultaneously collected and preprocessed. Participants receive feedback of their neural activity from an image of a thermometer with a dynamic bar level. Participants use this information to train themselves to self-regulate activity in specific brain regions, while associated behaviors are measured. Previous studies have demonstrated that real-time fMRI is effective in modulating physical pain-processing and associated rostral ACC activity,<sup>159</sup> emotional prosody-processing and associated IFG activity,<sup>160</sup> and negative emotion-processing and associated AI activity.<sup>161</sup> Future research should examine the efficacy of real-time fMRI on modulating neural patterns supporting mental state attribution, self-awareness, and empathy for non-physical pain, as well as enhancing social emotion-processing across typical development and clinical disorders.

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# Noninvasive remote activation of the ventral midbrain by transcranial direct current stimulation of prefrontal cortex

VS Chib<sup>1,2,5</sup>, K Yun<sup>1,2,5</sup>, H Takahashi<sup>3,4</sup> and S Shimojo<sup>1,2</sup>

The midbrain lies deep within the brain and has an important role in reward, motivation, movement and the pathophysiology of various neuropsychiatric disorders such as Parkinson's disease, schizophrenia, depression and addiction. To date, the primary means of acting on this region has been with pharmacological interventions or implanted electrodes. Here we introduce a new noninvasive brain stimulation technique that exploits the highly interconnected nature of the midbrain and prefrontal cortex to stimulate deep brain regions. Using transcranial direct current stimulation (tDCS) of the prefrontal cortex, we were able to remotely activate the interconnected midbrain and cause increases in participants' appraisals of facial attractiveness. Participants with more enhanced prefrontal/midbrain connectivity following stimulation exhibited greater increases in attractiveness ratings. These results illustrate that noninvasive direct stimulation of prefrontal cortex can induce neural activity in the distally connected midbrain, which directly effects behavior. Furthermore, these results suggest that this tDCS protocol could provide a promising approach to modulate midbrain functions that are disrupted in neuropsychiatric disorders.

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## Introduction

Dopaminergic neurons in the substantia nigra (SN) and ventral tegmental area (VTA) project to numerous areas in the brain.<sup>1–6</sup> Impairments in dopaminergic function of the SN/VTA (which we will collectively refer to as the ventral midbrain) have been implicated in the pathophysiology of a number of neurological and neuropsychiatric disorders such as Parkinson's disease, depression and addiction.<sup>7–10</sup> Given that SN/VTA neurons lie deep within the brain, the primary means of influencing them have been with systematic pharmacological interventions<sup>11</sup> or implantation of deep brain stimulators.<sup>12</sup> Systematic pharmacological intervention is the first line of therapy for many neurological and neuropsychiatric disorders;<sup>13</sup> however, it precludes from region-specific interventions, and some portions of patients with these disorders do not respond to the drug therapy. For such non-responders, invasive deep brain stimulation may be considered.<sup>14</sup>

The two predominant means of non-invasively stimulating the brain are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS).<sup>15</sup> TMS involves inducing an electrical current within the brain via a pulsating magnetic field applied by an induction coil stimulator placed above the scalp. tDCS involves the application of a small current between anodal and cathodal electrodes placed on the scalp. Both of these stimulation methods result in changes in brain function by causing neurons' resting membrane potential to depolarize or hyperpolarize. Positive stimulation

(as in the cases of TMS and anodal tDCS) causes a depolarization of the resting membrane potential, leading to increases in neuronal excitability and more spontaneous cell firing. Negative stimulation (in the cases of cathodal tDCS) causes hyperpolarization of the resting membrane potential, leading to decreases in neuronal excitability and decreased spontaneous cell firing. tDCS is generally applied in order to induce cortical changes that persist after stimulation, while TMS can be used to induce online cortical changes as well as changes that persist after stimulation. In both the cases, the duration and effects of stimulation increase as the duration of stimulation increases and the strength of the current increases. The benefits of tDCS over TMS, from a logistic therapeutic perspective, are that tDCS units are extremely inexpensive and easily mobile in comparison to TMS stimulators. For a thorough overview of tDCS, see Nitsche *et al.*<sup>16</sup>

tDCS and TMS have been used to probe neurocircuitry and treat neurological disorders in numerous studies.<sup>16–23</sup> Given that TMS and tDCS are only capable of stimulating the cortical surface, these studies have mainly focused on direct stimulation of a cortical region below the stimulation electrodes, rather than exploiting the interconnected neural network to induce remote changes in deep brain activity. It should be noted that two non-invasive brain stimulation studies reported cortical stimulation-induced activations in the caudate nucleus;<sup>24,25</sup> however, they are difficult to interpret as neither revealed functional connectivity that was

<sup>1</sup>Division of Biology, California Institute of Technology, Pasadena, CA, USA; <sup>2</sup>Computation and Neural Systems, California Institute of Technology, Pasadena, CA, USA; <sup>3</sup>Department of Psychiatry, Kyoto University Graduate School of Medicine, Kyoto, Japan and <sup>4</sup>Precursory Research for Embryonic Science and Technology (PRESTO), Japan Science and Technology Agency, Kawaguchi, Japan  
Correspondence: Dr VS Chib, Division of Biology, California Institute of Technology, 1200 E. California Boulevard, MC 139-74, Pasadena, CA 9128, USA.  
E-mail: vchib@caltech.edu

<sup>5</sup>These authors contributed equally to this work.

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directly related to stimulation-induced behavioral changes. More recently, a repetitive TMS study found that stimulation of motor cortex could induce changes in activity in the caudate and that stimulation-induced changes in connectivity between these areas were related to behavioral performance during a cognitive switching task.<sup>26</sup>

One recent study examining the effectiveness of anodal tDCS of frontal cortex in rodents found significantly increased neural activity in the frontal cortex and interconnected midbrain regions following stimulation.<sup>27</sup> Critically, the authors also found an increase in intracellular dopamine in these distal regions. They suggested that the increases in activity and intracellular dopamine in the midbrain were caused by the direct tDCS of the frontal cortex. This study alludes to the exciting possibility of exploiting the highly interconnected nature of cortical brain regions to stimulate deep brain dopaminergic areas that are not directly accessible with noninvasive stimulation methods. The results from this rodent study inspired us to test if such increased midbrain dopaminergic functions, in response to anodal tDCS of frontal cortex, could be induced using a similar paradigm in humans.

Given the superficial nature (that is, close to the cortical surface) of the prefrontal cortex, as well as its direct<sup>28–32</sup> and indirect efferent projections (via the striatum)<sup>5,33–35</sup> and functional synchrony<sup>36–38</sup> with the ventral midbrain, the ventromedial prefrontal cortex (VMPFC) and dorsolateral prefrontal cortex (DLPFC) struck us as excellent locations to directly stimulate to yield remote deep brain activity in humans. A number of studies have associated increases in VMPFC activity<sup>39–41</sup> and decreases in DLPFC activity,<sup>42–44</sup> with increases in midbrain activity and intracellular dopamine. Furthermore, DLPFC has been implicated in monitoring goal-directed behaviors and valuations that are encoded by the VMPFC.<sup>45–47</sup> With these relationships in mind, we hypothesized that excitatory/anodal and inhibitory/cathodal tDCS electrode placement over VMPFC and DLPFC, respectively, would result in the remote activation of the ventral midbrain. Moreover, we reasoned that cathodal stimulation of DLPFC would suppress its control over VMPFC, which would boost the anodal stimulation of the latter, and this enhanced VMPFC stimulation would yield an increased remote activation of the distally interconnected ventral midbrain. We further hypothesized that this remote activation would manifest behaviorally as increases in participants' rewarding appraisals. We chose this behavioral task because discrimination of facial attractiveness and emotions are commonly disrupted in neuropsychiatric disorders such as depression, schizophrenia and Parkinson's disease).<sup>48–51</sup>

## Materials and methods

**Participants.** Ninety-nine right-handed healthy participants took part in this experiment (mean age,  $22.9 \pm 3.95$  years; range 18–37 years), of which 47 were female. Participants had no history of neurological or psychiatric illness. The California Institute of Technology Review Board approved this study, and all participants gave informed consent.

**Stimuli.** Participants made attractiveness ratings of a series of 140 faces generated with computer software (FaceGen;

Singular Inversions, Toronto, ON, Canada). Seventy male and 70 female Caucasian/European neutrally expressive faces were randomly constructed. The attractiveness of these faces was rated on an eight-point scale ranging from 0 to 7.

Before the experiment, we had a separate group of observers rate these faces ( $n = 20$ ). Based on these ratings, we divided the series of 140 faces into two sets. Using the preliminary ratings, we made sure these two groups of faces were uniformly distributed across the range of attractiveness and had the same means and s.d.s. of attractiveness ratings (before-stimulation set:  $3.66 \pm 1.00$ ; after-stimulation set:  $3.66 \pm 1.02$ ). These attractiveness-balanced sets of faces allowed us to control for possible mere exposure effects that could occur if the same set of faces were used before and after stimulation.

**Experimental protocol.** The experiment was divided into three sessions. During the first session (before stimulation), participants made facial attractiveness judgements. During the second session, participants were stimulated with tDCS for 15 min. Finally, during the final session (after stimulation), participants again made facial attractiveness judgments.

To assess the behavioral effects of tDCS, participants were asked to make attractiveness ratings of faces. As described above, two sets of attractiveness-balanced faces were used. One served as a before-stimulation test set, the other an after-stimulation test set. The faces in each set were presented in randomized order. In every trial, participants were presented with a face to rate the attractiveness on an eight-point scale. Participants made a rating by selecting one of the eight buttons on two button-press response pads. One response pad was placed in each hand of the participant, and ratings progressed from the left hand fourth phalange being 0 to the right hand fourth phalange being 7. Participants had 4 s to make a rating, after which their rating value was presented to them for 1 s, followed by a pseudorandomly ( $\sim 1$ – $10$  s) jittered blank screen. Trials in which subjects did not make a selection in the allotted time were assigned as 'missed responses'.

To assess the neural effects of tDCS, the two groups of participants were scanned with functional magnetic resonance imaging (fMRI) while making facial attractiveness ratings. These participants were removed from the scanner during administration of tDCS.

**fMRI data acquisition.** Functional imaging was conducted using a 3.0 Tesla Trio MRI scanner to acquire gradient echo T2\*-weighted echoplanar (EPI) images with blood oxygenation-level-dependent (BOLD) contrast. To optimize functional sensitivity in the frontal cortex, a key region of interest (ROI), we acquired the images in an oblique orientation of  $30^\circ$  to the anterior commissure–posterior commissure line.<sup>52</sup> In addition, we used a 12-channel-phased array coil to boost the MRI signal. Each volume of images had 44 axial slices. The imaging parameters were as follows: echo time, 30 ms; field of view,  $192 \text{ mm}^2$ ; in-plane resolution and slice thickness 3 mm (no gap); repetition time, 2.75 s. Whole-brain high-resolution T1-weighted structural scans ( $1 \times 1 \times 1 \text{ mm}^3$ ) were acquired for each participant, coregistered with their mean EPI images and averaged across participants to permit anatomical localization of the functional activations at the group level.

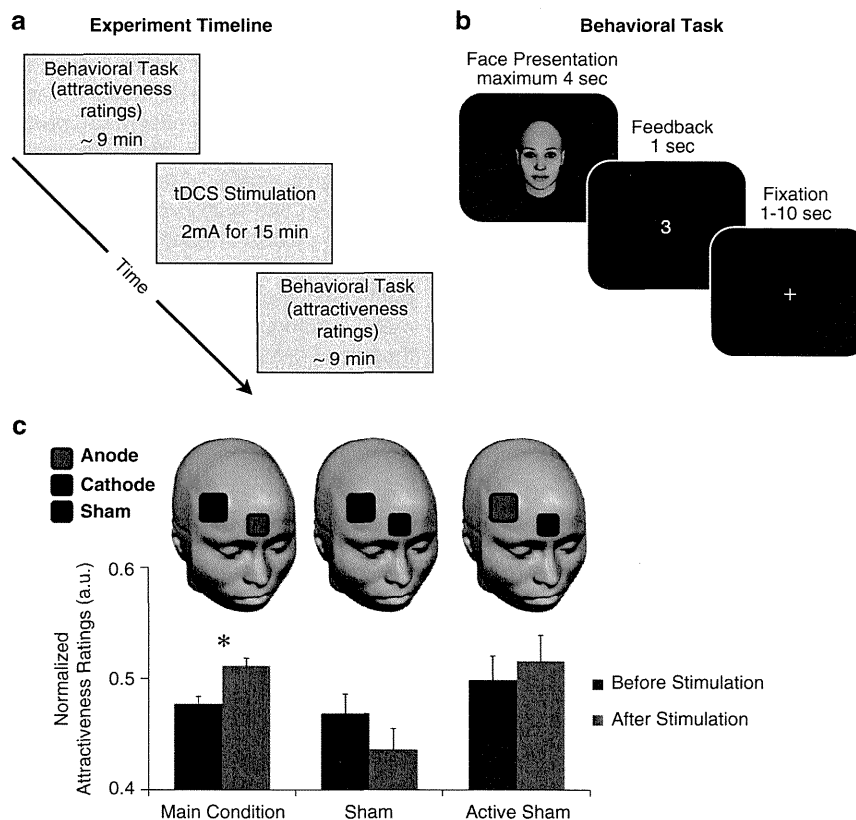
**tDCS administration.** tDCS was delivered using a battery-driven constant-current stimulator (DC-Stimulator, neuroConn GmbH, Ilmenau, Germany), through conductive-rubber electrodes, placed over two saline-soaked sponges. To allow for more focal stimulation in the main stimulation condition (anode placement over VMPFC, cathode placement over DLPFC), we used two sizes of electrode.<sup>53</sup> In the main condition, the smaller-sized electrode was 3.5 cm × 3.5 cm (12.25 cm<sup>2</sup>, current density, 0.16 mA cm<sup>-2</sup>) and placed over VMPFC, and the larger-sized electrode was 5 cm × 5 cm (25 cm<sup>2</sup>, current density, 0.08 mA cm<sup>-2</sup>) and placed over DLPFC. Figure 1c and Supplementary Figure S1 show an illustration of the electrode placements in all stimulation conditions.

During active stimulation conditions, tDCS was performed for 15 min and at 2 mA intensity (20 s ramp in and 20 s ramp out). The impedance was controlled by the device, normally ranging < 10 kΩ, limited by the voltage at < 26 V. Similar stimulation parameters are commonly used to elicit behavioral responses from tDCS.<sup>16</sup>

We localized stimulation sites using a combination of the 10–20 international system for EEG placement and

anatomical landmarks. Our experiment involved four stimulation sites of interest (VMPFC, right DLPFC, left DLPFC, vertex). To stimulate the VMPFC, we placed an electrode with its center halfway between Fp1 and Fp2 and over the glabella. To stimulate the right and left DLPFC, we placed an electrode over F4 and F3, respectively. This method of DLPFC localization has been used in tDCS and TMS studies,<sup>54–57</sup> and has been confirmed as an accurate method of localization.<sup>58</sup> To stimulate the vertex, we placed an electrode over the center of Cz. Given tDCS's low spatial resolution and diffuse current spread, it is common to localize stimulation locations using EEG landmarks as opposed to participant-specific neuroanatomy.

We stimulated with six different electrode orientations: Group 1/Main Stimulation Group (*N* = 19, 6 females): The anode was placed above the VMPFC and the cathode above the right DLPFC. Group 2/Sham Stimulation Group (*N* = 20, 8 females): No stimulation was delivered and electrodes were placed in the same locations as Group 1. Group 3/Active Sham Group (*N* = 16, 6 females): The anode was placed above the right DLPFC and the cathode above the VMPFC.



**Figure 1** Experimental setup and behavioral results. (a) The experiment can be divided into three sessions. During the first session (before stimulation), participants made facial attractiveness judgements. During the second session, participants were stimulated with transcranial direct current stimulation (tDCS) for 15 min. During the final session (after stimulation) participants again made facial attractiveness judgements. The main and active sham groups were scanned with functional magnetic resonance imaging during the before and after stimulation sessions and were removed from the scanner during stimulation. (b) At the beginning of each trial of the behavioral task, participants were shown a face and made a rating of how attractive they found the face on a scale from 0–7; 0 being not attractive at all and 7 being very attractive. (c) Anodal stimulation of the ventromedial prefrontal cortex (VMPFC) and cathodal stimulation of the right dorsolateral prefrontal cortex (DLPFC) (main stimulation group) resulted in a significant increase in mean attractiveness ratings ( $*P < 0.05$ ). We performed a number of control conditions on separate groups of participants, none of which resulted in a significant increase in attractiveness ratings (For a complete description of the control results, see Supplementary Figure S1). To allow for a more focal stimulation of VMPFC in the main group, we administered tDCS with a small electrode over VMPFC and a large electrode over DLPFC. Error bars denote s.e.m. a.u., arbitrary units.

Group 4 ( $N = 15$ , 7 females): The anode was placed above the VMPFC and the cathode above the vertex with the center of Cz. Group 5 ( $N = 15$ , 10 females): The anode was placed above the vertex and the cathode above the right DLPFC. Group 6 ( $N = 14$ , 10 females): The anode was placed above the VMPFC and the cathode above the left DLPFC. Participants felt the current as an itching sensation at both electrodes during stimulation. Some participants reported feeling no sensations resulting from stimulation.

We performed these control conditions to confirm that the effects of anodal tDCS of VMPFC and cathodal tDCS of DLPFC (Group 1, main stimulation condition) were specific to this stimulation orientation and polarity. The only condition that resulted in a significant increase in attractiveness ratings was the main stimulation condition (results of all the stimulation groups are shown in Supplementary Figure S1).

We scanned participants in Groups 1 (main stimulation group) and 2 (active sham group) with fMRI during the sessions in which they made attractiveness ratings. We focused our imaging analysis on these two groups to examine the neural effects of the main condition as compared with a control stimulation group that mirrored the main stimulation condition without resulting in a significant behavioral effect. Participants in these groups were removed from the fMRI scanner during the stimulation. This allowed us to examine tDCS-induced changes in neural function associated with significant behavioral changes (main group), as compared with a control stimulation condition that did not result in a significant behavioral effect (active sham group).

**Behavioral data analysis.** Raw attractiveness ratings were skewed toward zero. We used max-normalization of the ratings (dividing participants ratings by their maximum attractiveness rating). This normalization allowed us to correct for participants' use of abbreviated ranges of the rating scale. To confirm that the rating data was normal, we performed a Kolmogorov–Smirnov test (before stimulation:  $P = 0.163$ ; after stimulation:  $P = 0.20$ ).

We used analysis of variance for repeated measures to investigate whether there was a difference between before/after stimulation and the various stimulation groups. Planned comparisons were performed using paired  $t$ -tests to investigate whether there was a difference between before- and after-stimulation conditions in each group.

**fMRI preprocessing.** Image analysis was performed using SPM8 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK). Images were corrected for slice acquisition time within each volume, motion corrected with realignment to the first volume, spatially normalized to the standard Montreal Neurological Institute EPI template and spatially smoothed using a Gaussian kernel with a full width at half maximum of 8 mm. Intensity normalization and high-pass temporal filtering (using a filter width of 128 s) were also applied to the data.

**fMRI general linear model (GLM).** To analyze the data, we estimated participant-specific (first-level) GLMs using a first-order autoregressive model. This model was designed to

identify regions in which BOLD activity was parametrically related to attractiveness ratings and was estimated for the experiment phases in which participants made attractiveness ratings. The GLM included the following regressors for each stimulation condition (before/after stimulation):

1. An indicator function denoting a rating trial, and
2. An indicator function denoting a rating trial multiplied (that is, modulated) by the participants' rating value (0–7 scale) for the face presented in the trial.

Both regressors were modeled as stick functions at the onset of stimulus presentation. The model also included motion parameters, session constants and missed trials as regressors of no interest. The regressors of interest and missed trial regressor were convolved with a canonical form of the hemodynamic response.

This GLM also made use of a parametric regressor. These types of regressors look for areas in which the BOLD response varies with the magnitude of a variable of interest (in this case the attractiveness rating). The estimated coefficient for such regressors can be roughly interpreted as a measure of the strength of association between the BOLD response and the variable of interest.

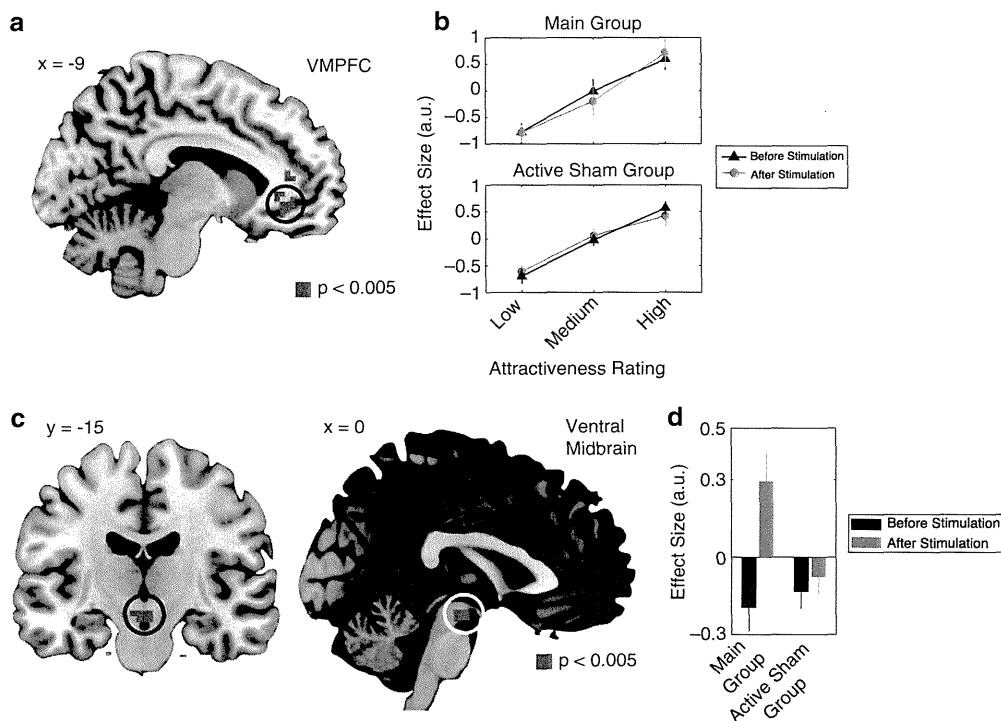
Single participant contrasts were calculated for the rating parametric regressor separately for the before- and after-stimulation conditions. These contrasts were motivated by previous work and identified regions where BOLD activity is correlated with attractiveness ratings.<sup>59,60</sup> We also calculated single participant contrasts for the difference between the parametric regressor for the after-stimulation and before-stimulation conditions. This contrast identifies regions where BOLD activity is more correlated with attractiveness ratings after stimulation than before.

**Group-level analysis.** The contrast images computed for each participant were taken to the group random effects level, and conjunctions and comparisons were conducted between Group 1 (main stimulation group) and Group 2 (active sham group) to determine areas showing tDCS-induced changes in activity.

We computed a conjunction contrast to identify brain areas with overlapping correlations with attractiveness ratings before and after stimulation in both the main and the active sham groups (Figure 2a). We also computed an interaction contrast between attractiveness ratings and before/after stimulation (Figure 2c). For this interaction, we examined differences in activity between the main and active sham groups.

For visualization purposes only, all of the images shown are thresholded at  $P < 0.005$ . For inference purposes, the tables in the Supplementary Information report those areas within *a priori* regions of interest that survive false discovery rate correction. ROI definitions are described below.

**Psychophysiological interactions (PPIs).** The goal of this analysis was to investigate whether anodal tDCS of VMPFC, and simultaneous cathodal tDCS of DLPFC (main stimulation group), caused an increase in the correlation between



**Figure 2** Functional magnetic resonance imaging results. (a) A common region of the ventromedial prefrontal cortex (VMPFC) in which activity correlated with attractiveness ratings before and after stimulation, in both the main group and the active sham group. (b) The effect size in the VMPFC increased with attractiveness ratings (lower—lower tertile; medium—middle tertile; high—upper tertile). (c) An interaction contrast between attractiveness ratings and stimulation revealed a significant increase in ventral midbrain activity in the main group as compared with the active sham group. (d) For the interaction contrast, average effect sizes representing the correlation between ventral midbrain activity and rating values before and after stimulation in the main and active sham groups. Ventral midbrain activity was positively correlated with attractiveness ratings after administration of transcranial direct current stimulation. All contrasts are displayed at  $P < 0.005$  uncorrected, and significant at  $P < 0.05$ , small volume corrected. a.u., arbitrary units.

VMPFC activity and activity in the ventral midbrain compared with the active sham group.

The analysis proceeded in three steps:

First, we computed individual average time series within a 6-mm sphere surrounding individual participant peaks (in both the main and active sham groups) within the functional mask of VMPFC shown in Figure 2a. Variance associated with the six motion regressors was removed from the extracted time series. The location of the peak voxels was based on the GLM described above. The seed time courses were deconvolved, based on the formula for the canonical hemodynamic response, in order to construct a time series of neural activity in the left VMPFC. This was done following the procedures described in Gitelman *et al.*<sup>61</sup>

Second, we estimated a GLM with the following regressors:

1. An interaction between the neural activity in the seed region and an indicator function for before-stimulation and after-stimulation trials,
2. An indicator function for before-stimulation and after-stimulation trials, and
3. The original BOLD eigenvariate (that is, the average time series from the 6-mm sphere).

The first two regressors were convolved with a canonical form of the hemodynamic response function, and the model

also included motion parameters as regressors of no interest. The first regressor in this PPI identifies areas that exhibit stimulation-related functional connectivity with VMPFC. In particular, it identifies areas in which the correlation in BOLD activity with VMPFC increases after tDCS. It is important to note that this PPI analysis did not include participants' behavioral ratings and thus revealed neural responses irrespective of the behavioral results.

Third, single participant contrasts for the first regressor were calculated, and a second-level analysis was performed by calculating the main and active sham groups' contrast coefficients.

**Post-hoc between-participant regressions.** To explore the results further, we performed *post-hoc* linear regressions for the main and active sham groups. We regressed a behavioral measure of the influence tDCS had on attractiveness ratings with a neural measure of the impact tDCS had on connectivity between VMPFC and ventral midbrain, separately for the main and active sham groups. The behavioral measure was calculated by subtracting average ratings of before stimulation from those of after stimulation. The neural measure was the average parameter estimate extracted from the anatomical ROI in the ventral midbrain from the PPI, separately for each stimulation group (main and active sham).