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ORIGINAL INVESTIGATION

A single dose of antidepressant alters eye-gaze patterns across face stimuli in healthy women

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Abstract
Background Early neurocognitive changes in emotional processing are seen following SSRI administration, which may be involved in mechanisms of action. However, the perceptual processes underpinning these effects have not been specified.
Methods In a double-blind, placebo-controlled eye-tracking study, we assessed the effect of single dose of citalopram (20 mg) in 25 healthy females. Face stimuli with direct and averted gaze were presented while visual scan patterns and pupil sizes were monitored. Subjective state was monitored using visual analogue scales.
Results There were no significant effects of citalopram on subjective state. However, the citalopram group displayed increased saccade numbers and shorter fixation duration during face viewing compared to the placebo group. Volunteers receiving citalopram also showed reduced monitoring of the eye region irrespective of the direct or averted eye position of the stimuli. The citalopram group also showed significantly larger pupil sizes than the control group.
Conclusions These results suggest that the SSRI administration affects the perceptual processing of face stimuli. The current pattern of findings is consistent with anxiogenic-like mechanisms early on in SSRI treatment. Eye-tracking provides a novel method to characterise and detect these effects.

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Introduction

Although current pharmacological treatments for depression and anxiety are commonly prescribed, we still lack critical information about their mechanisms of action. A growing evidence suggests that antidepressant administration (AD) can target negative affective biases seen in depression. For example, short-term treatment with the SSRI citalopram reduces the recognition of negative facial expressions of emotion, improves positive affective memory and reduces the emotion-potentiated startle response. These changes take place in the absence of significant differences in ratings of mood and anxiety (Grillon et al. 2009, 2007; Harmer et al. 2004). Such early effects have been hypothesised to reverse the negative biases seen in depression on these measures and play a role in the gradual improvement in mood and symptoms over time as the patient responds to this more positive perspective (Harmer et al. 2009). By contrast, acute administration of citalopram can have the paradoxical effect of increasing anxiogenic-like responses. Thus, acute administration of citalopram in healthy volunteers enhances the recognition of fearful facial expressions (Harmer et al. 2003) and increases reactivity in an emotion-potentiated startle task (Browning et al. 2007). Such findings are consistent with clinical observations of increased anxiety early on in SSRI treatment that reverses with continued administration. The neurocognitive perceptual mechanisms that underlie altered emotion processing after acute AD are unknown.

Eye-tracking is a highly sensitive, non-intrusive procedure that enables the study of neurocognitive processes early in the information processing pathways, i.e. in visual perception and attention. Although covert attention can be controlled independently of (overt) eye movements, the control of eye-gaze patterns and attention are closely coupled during attention shifts (Henderson 1992). Humans tend to scan human faces predominantly by focusing on the eyes, the nose and the mouth regions (Kelly et al. 2010; Walker-Smith et al. 2013). The eye and the mouth regions provide the most important visual cues for facial emotion identification, and people fixate more on these regions when asked to evaluate other's emotional states (Malcolm et al. 2008). Eye-tracking has been used successfully to illuminate perceptual processes that might underlie changes in face perception after brain lesions involving the amygdala (Adolphs et al. 2005) and in psychological disorders (Holzman et al. 1973). A recent study suggests that high neuroticism (with increased trait vulnerability to depression) is associated with avoidance of the eye area of facial stimuli irrespective of the facial expressions of emotion including neutral, fearful and happy cues (Di Simplicio et al. 2014). Such effects may represent an attempt to reduce the impact of socially relevant cues in this highly anxious group, consistent with previous reports in social anxiety (Horley et al. 2003). This avoidance may be seen across face stimuli in general, irrespective of emotional valence, if all such stimuli are perceived as of potential threat value (Horley et al. 2003). Consistent with this interpretation, the visual exploration of face stimuli is increased by repeated antidepressant treatment in participants with high levels of neuroticism (Di Simplicio et al. 2014). Eye gaze has also been shown to be sensitive to antidepressant treatment in patients with depression (Wells et al. 2014).

The current study therefore used eye-tracking techniques to evaluate how volunteers process neutral face stimuli following a single dose of the SSRI citalopram. Face stimuli were presented with direct versus averted eye gaze which can modulate mechanisms of threat detection (George et al. 2001). We also collected data on pupil size since this measure is sensitive not only to emotionally relevant stimuli but also to other fundamental cognitive mechanisms like load on attentional capacity (Laeng et al. 2012). Females were selected to reduce variability associated with gender differences in the pharmacokinetics and pharmacodynamics of antidepressants (Keers and Aitchison 2010). We predicted that acute administration of citalopram would alter visual scan patterns for neutral face stimuli. Consistent with reduced attention to the eye region in anxiety (Di Simplicio et al. 2014; Horley et al. 2003), we predicted reduced visual attention to the eye area, especially to eyes with direct gaze following citalopram. As a secondary aim, we explored the associations between pupil sizes and drug intervention.

Methods

Subjects and context Twenty-five healthy female participants between 19 and 29 years old (M=22.5, SD=2.8) were randomised to receive either a placebo or citalopram. Exclusion criteria were the following: former and/or actual psychological disorder, neurological disorder, current medication against somatic or psychological disorders and pregnancy. Visual analogue scales were used to measure current subjective mood and fatigue before and after individual test sessions. Current mood related to anxiety, depression, irritability and fatigue vas rated on 7-point scales. All participants were given information about the aim of the study, known side effects of citalopram and provided consent. Citalopram 20 mg or placebo was given per oral in a double-blind design 3 h prior to eye-gaze data acquisition. Both placebo and citalopram pills were covered by a citrus-flavoured expanse to ensure similar taste and appearance. The experimental procedures were approved by the Regional Ethics Committee (2011/1337/REK sør-øst D) and were completed at the Department of Psychology at the University of Oslo, Norway. One of the participants from the citalopram group did not complete the eye-tracking procedure due to technical constraints (malfunction of hardware), leaving 12 participants in each group.

Stimuli Colour photographs of 21 young females and 21 young males, with neutral face expressions, and direct or averted gaze were selected from the Oslo Face Database. The order of presentation was pseudo-randomised. Each image (19.5×19.5 cm) was presented on a computer screen located about 70 cm in front of the participant, with a resolution of 1,680×1,050 pixels. The models' heads in the images subtended about 9.8×13° of visual angle. A baseline image with a fixation point, placed in any of the four corners of the image to avoid any central bias from the initial fixation, was presented prior to each facial stimulus.

The face eye-tracking task After presentation of a fixation point that appeared randomly in one of the four corners of the baseline image for 2,000 ms, a facial image was presented on the computer screen for 5,000 ms. This was followed by presentation of a visual analog scale for a maximum of 10 s. To facilitate the visual exploration of the stimuli, participants were instructed to rate how attractive each face was on a scale ranging from 0 (very unattractive) to 10 (very attractive). After the response (or when 10 s elapsed), another baseline image was presented, followed by another facial image, then by the visual analog scale, etc. The total duration of the task was approximately 5 min (Fig. 1).

Eye-tracking procedure and analyses Eye-gaze data were sampled on the SMI RED250 remote eye-tracking device.

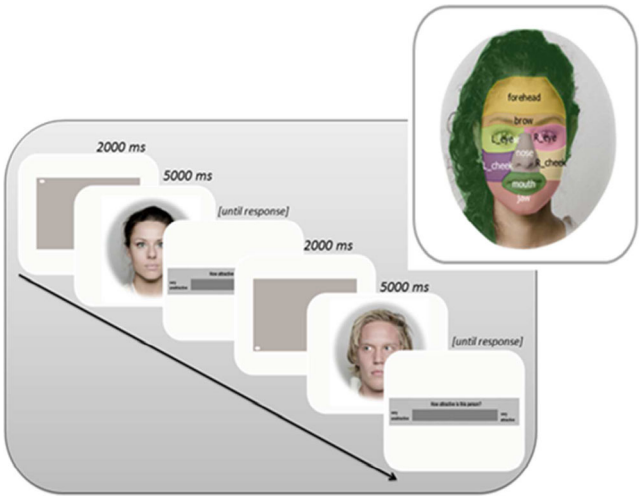

Fig. 1 Forty-two images of human faces were presented after a 2,000 ms inter-stimulus fixation point. A visual analogue scale was shown below the stimulus images after 5,000 ms. The areas of interest (AOIs) used in the analysis are illustrated in the *top right corner*

The number of saccades (mean) and fixation duration were computed for the face stimuli using SMI BeGaze software. All data were sampled under the same light conditions and included a calibration procedure. Blink detection and eye-gaze dispersion were extracted as potential sources of random error. Minimum fixation duration defines the minimum time window in which the gaze data is analysed. Event detection preprocessing parameters were set to fixation-based algorithm with minimum fixation duration set to the default 80 ms. The algorithm identifies fixation as groups of consecutive points within a particular dispersion. Maximum dispersion was set to 100 px. Pupillometric fixation data (average pupil diameter) were separately sampled from individual fixations for the initial fixation points and the face stimuli.

Procedures and analysis All data were analysed by the use of IBM's SPSS 20. Analyses of variance (ANOVA) for repeated measures were used to explore potential differences in ratings of subjective mood and fatigue and the potential interactions with the citalopram intervention. A single *t* test was used to explore group differences in stimulus attractiveness. A two-way ANOVA was used to explore the potential general differences in eye-gaze patterns during viewing of face stimuli (5,000 ms) between the citalopram group and placebo. Areas of interest (AOI) were created individually for each of the faces: eyes (left and right), nose, mouth, cheeks (left and right), eyebrows, jaw, forehead, hair and the rest (white space). AOI eye movement data (fixation time to AOIs) were analysed in a two-way ANOVA. Average pupil diameters were compared between stimulus types (face stimulus versus fixation point) and drug type (citalopram or placebo) in two-way ANOVAs.

Results

Behavioural data There was no statistically significant main effects on the scores for irritability [F(1, 23)=.143, p=.708; Wilk's Λ=.994] or any interaction between irritability and drug intervention [F(1, 23)=.143, p=.708; Wilk's Λ=.994]. No main effect of the scores for anxiety [F(1, 23)=.911, p=.350; Wilk's Λ=.962] was found together with no interaction with the intervention [F(1, 23)=.010, p=.922; Wilk's Λ=1.00]. Similarly, no main effect of the scores for depressed mood [F(1, 23)=.854, p=.365; Wilk's Λ=.964] or interaction with the intervention was found [F(1, 23)=.281, p=.601; Wilk's Λ=.988]. On the other hand, fatigue levels were higher at the time of eye-gaze data acquisition (M=3.88, SD=1.32) compared to 3 h before (M=3.16, SD=1.18) at the time of the drug administration [F(1. 23)=6.617, p=.017; Wilk's Λ=.777, η^2=.22]. This main effect did not differ between the two groups [F(1, 23)=.585, p=.452; Wilk's Λ=.975]. Finally, no difference was found between the citalopram and placebo groups in mean ratings of face attractiveness [t(1.23)=1.048, p=.305].

Eye movement data The analysis revealed significant group differences between the placebo and the citalopram groups on the number of saccades [F(1, 22)=5.164, η^2=.18, p=.033] and mean fixation duration [F(1, 22)=6.276, η^2=.21, p=.020]. Post hoc analysis that excluded potential outliers based on deviations from the 50 percentile (1.5 box plot length) had minimal impact on these general findings (Fig. 2). The two groups did not differ in two measures of potential error sources: average dispersion [F(1, 22)=.516, p=.480] and average blinks [F(1, 22)=190, p=.667].

AOI eye movements data We assessed the percentage of fixation time spent looking at different regions of the faces. This analysis revealed that participants fixated longest on the eye region, followed by the nose and mouth regions, consistent with the predicted gaze pattern to faces [F (1, 22)=40.44, p<.001; Wilk's Λ=.044, η^2=.95]. Importantly, a pronounced decrease in fixation time to the eye region was observed with citalopram [F (1, 22)=5.34, p=.031, η^2=.20] (Fig. 3a). Fixations towards other AOIs did not differ statistically between citalopram and placebo. The temporal pattern of this general effect revealed statistically significant differences over the first 500, 1,000 and 5,000 ms after stimulus onset for the eye region [F (1, 22)=36.86, p<.001, η^2=.77] but no interaction between this factor and drug intervention [F (1, 22)=.92, p=.42]. Thus, generally, despite more fixations towards the eye region in the later phases of the stimulus presentation, the citalopram group disengaged from the eye region in all the three phases of the face stimulus presentation (Fig. 3b).

There was a general main effect of eye-gaze direction. Both groups looked more at face stimuli with a direct gaze [F (1,

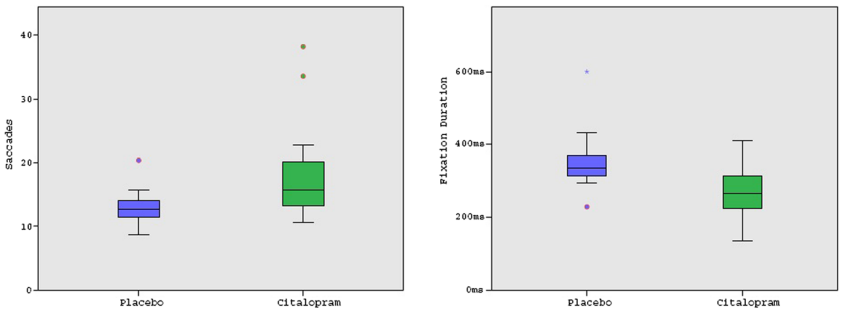

Fig. 2 The box plots shows eye-gaze data for saccades and fixation duration estimated from the placebo versus citalopram intervention

22)=7.80, Wilk's Λ=.738, p=.011, η^2=.26], but no interaction with the drug intervention was found [F (1, 22)=2.73, Wilk's Λ=.890, p=.113].

Pupil size data Pupillometric analysis revealed a statistically significant main effect of the drug intervention on average pupil sizes [F (1, 22)=16.32, p<.001, η^2=.42]. The citalopram group had larger pupil sizes during both face stimuli (M=4.52/3.76) and during the fixation points (M=4.53/3.82) compared to the placebo.

Discussion

The main findings from the current study confirm that a single oral dose of citalopram (20 mg) is associated with pronounced differences in neurofunctional measures such as visual perception and attention. Specifically, citalopram ingestion resulted in more extended face exploration as illustrated by shorter fixations and increased number of saccades to the faces. Although the overall pattern of gaze to the faces remained the same (i.e. they still looked most at the eyes), we observed decreases in the fixation times to the eyes with citalopram compared to placebo. A possible reactive eye-gaze pattern was explored by temporal segregations of the face stimuli presentations. Temporal analysis demonstrated that a difference between the two groups was detectable early (500 ms) after stimulus presentation and lasted for the whole duration of stimulus presentation. Contrary to our hypothesis, however, this effect was not modulated by direct versus averted gaze of the facial stimuli. The citalopram group also showed stimulus-independent increases in pupil sizes compared to placebo. All these effects occurred in the absence of drug-induced changes in ratings of subjective state or ratings of facial attractiveness.

These results provide further evidence for differences in processing of salient social face stimuli after acute SSRI administration. Both participants high on trait anxiety and those diagnosed with generalised anxiety disorder orient to threatening faces compared to neutral faces by "hyper-scanning" the face stimuli employing more fixations and saccades (Bradley et al. 2000). Anxiety is also associated with fixation instability (Laretzaki et al. 2011). When presented to alternative stimulus categories, individuals high on trait anxiety make more saccades to the eye region of fearful faces compared to sad and happy faces (Perlman et al. 2009). Eye contact with emotional faces is highly arousing to the viewer (Adams et al. 2003; Whalen et al. 2004), and disengaging from the eyes may therefore serve as an adaptive emotion-regulative mechanism by moderating trait congruent information processing. Acute administration of citalopram appeared to emulate this eye-gaze pattern and increased the number of saccades across the neutral faces, while reducing gaze over the eye region in healthy females. The results were present in the absence of self-reported mood or subjective state changes. As such, these effects suggest an effect of citalopram on the processing of social cues, which may be relevant to the effects of SSRIs on emotion processing. The increased pupil sizes in the citalopram group may reflect a physiological effect of the

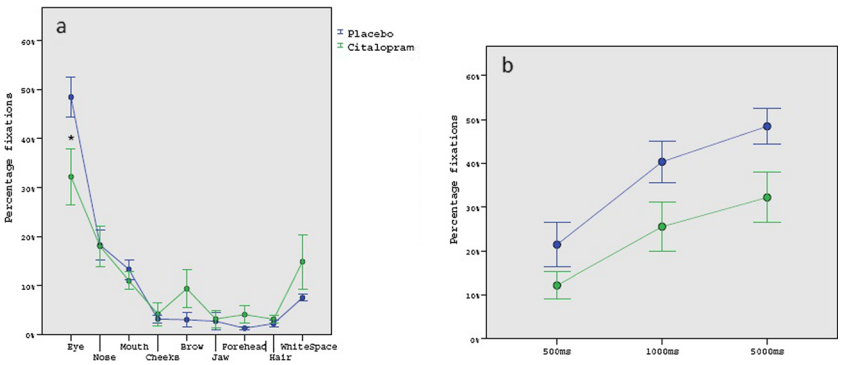

Fig. 3 **a** Percentage fixation time to faces as a function of AOI and pharmacological intervention (*p<.05). **b** Fixations towards the eye region from the first 500, 1,000 and 5,000 ms. *Error bars* represent ±1SE

drug (see Dumont et al. 2005). Alternatively, attentional load caused by increased attentional monitoring of threat-relevant stimuli may have caused the differences in pupil sizes in citalopram versus placebo.

Although volunteers did not report feeling more anxiety or agitation after treatment, eye-tracking may provide a more sensitive marker of mechanisms engaged by pharmacological manipulations, which are not always available to conscious awareness. This anxiogenic-like response is consistent with several previous studies on acute SSRI administration in healthy volunteers. Citalopram tends to increase reactivity in emotion-potentiated startle paradigms (Browning et al. 2007; Harmer et al. 2003) and increase the labelling of facial cues as fearful (Harmer et al. 2003). Recently, Simonsen et al. (2014) showed that females receiving citalopram rated face stimuli less trustworthy compared to placebo. Acute citalopram administration may increase alertness towards emotionally salient environmental stimuli like neutral human faces. As such, our findings provide a perceptual basal mechanism that may be involved in adaptive emotional processing after AD therapy. Using fMRI, a number of studies have demonstrated changes in the neural processing emotional stimuli after short time administration of antidepressants or placebo (see Harmer et al. 2009). The changes took place in the absence of significant differences in ratings of mood and anxiety and revealed an adaptive activation pattern in a recall condition. Longer fixation duration for emotional faces has recently been observed in both current and former depression (Isaac et al. 2014). Early anxiogenic-like response in AD therapy is often experienced as undesirable side effects, but may facilitate adaptive modification of information processing in a manner which would be expected to reverse biased attention in MDD.

Combination therapies, by the use of multiple pharmacological agents, have been used to enhance therapeutic outcome in MDD (Stahl 2010). Some combinations include SSRI plus a beta-blocker, SSRI plus atypical antipsychotics or SSRI plus the NMDA receptor antagonist ketamine or evolving multimodal antidepressants like vilazodone and vortioxetine. Eye-tracking appears to be a sensitive method for exploring effects of AD and may therefore serve as an important tool in the development and evaluation of efficacy in new antidepressants and combination therapies.

Our study had a number of limitations. The processing of face stimuli may be modulated by selective spatial attention or may be conditional on the participant's intentional goals and general understanding of the task (Buttle 2010). Our study asked the volunteers to rate facial attractiveness to maintain attention to the face stimulus. However, it is unknown whether a similar profile of effects from citalopram treatment would be observed with emotional faces or with a different instruction. Studies including active control medications could further elucidate the unique moderation by acute citalopram versus other monoaminergic agents. The restricted age cohort and inclusion of only females may have contributed to the pronounced effects reported in our study. Generalisation of these results to different groups needs to be tested.

Conclusion

The present study provides evidence for altered visual scan patterns after acute SSRI treatment. The data support the hypothesis that antidepressants have early effects on emotional processing in a manner that may contribute to some clinical effects in depression and anxiety. Eye-tracking of salient social stimuli provides a novel and sensitive way of characterising and understanding current and evolving antidepressant and anxiolytic treatment effects.

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Ethical statement The manuscript meets the guidelines for ethical conduct and report of research www.elsevier.com/wps/find/authorsview.authors/rights.

Conflict of interest The authors report no direct conflict of interests.

References

Adams RB, Gordon HL, Baird AA, Ambady N, Kleck RE (2003) Effects of gaze on amygdala sensitivity to anger and fear faces. Science 300: 1536–1536

Adolphs R, Gosselin F, Buchanan TW, Tranel D, Schyns P, Damasio AR (2005) A mechanism for impaired fear recognition after amygdala damage. Nature 433:68–72

Bradley BP, Mogg K, Millar NH (2000) Covert and overt orienting of attention to emotional faces in anxiety. Cogn Emot 14:789–808

Browning M, Reid C, Cowen PJ, Goodwin GM, Harmer CJ (2007) A single dose of citalopram increases fear recognition in healthy subjects. J Psychopharmacol 21:684–690

Buttle H (2010) Repetition blindness for faces reflects identity coding but not emotion coding. Percept Mot Skills 110:245–256

Di Simplicio M, Doallo S, Costolini G, Rohenkohl G, Nobre G, Harmer CJ (2014) Can you look me in the face? Short-term SSRI administration reverts avoidant ocular face exploration in subjects at risk for psychopathology. Neuropsychopharmacology. doi:10.1038/npp.2014.159

Dumont GJ, de Visser SJ, Cohen AF, van Gerven JM, Biomarker Working Group of the German Association for Applied Human P (2005) Biomarkers for the effects of selective serotonin reuptake inhibitors (SSRIs) in healthy subjects. Br J Clin Pharmacol 59:495–510

George N, Driver J, Dolan RJ (2001) Seen gaze-direction modulates fusiform activity and its coupling with other brain areas during face processing. Neuroimage 13:1102–1112

Grillon C, Levenson J, Pine DS (2007) A single dose of the selective serotonin reuptake inhibitor citalopram exacerbates anxiety in humans: a fear-potentiated startle study. Neuropsychopharmacology 32:225–231

Grillon C, Chavis C, Covington MF, Pine DS (2009) Two-week treatment with the selective serotonin reuptake inhibitor citalopram reduces contextual anxiety but not cued fear in healthy volunteers: a fear-potentiated startle study. Neuropsychopharmacology 34:964–971

Harmer CJ, Bhagwagar Z, Perrett DI, Vollm BA, Cowen PJ, Goodwin GM (2003) Acute SSRI administration affects the processing of social cues in healthy volunteers. Neuropsychopharmacology 28: 148–152

Harmer CJ, Shelley NC, Cowen PJ, Goodwin GM (2004) Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. Am J Psychiatry 161:1256–1263

Harmer CJ, Goodwin GM, Cowen PJ (2009) Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. Br J Psychiatry 195:102–108

Henderson J (1992) Visual attention and eye movement control during reading and picture viewing. In: Rayner K (ed) Eye movements and visual Cognition (Springer Series in Neuropsychology). Springer, New York, pp 260–283

Holzman PS, Proctor LR, Hughes DW (1973) Eye-tracking patterns in schizophrenia. Science 181:179–181

Horley K, Williams LM, Gonsalvez C, Gordon E (2003) Social phobics do not see eye to eye: a visual scanpath study of emotional expression processing. J Anxiety Disord 17:33–34

Isaac L, Vrijsen JN, Rinck M, Speckens A, Becker ES (2014) Shorter gaze duration for happy faces in current but not remitted depression: evidence from eye movements. Psychiatry Res 218: 79–86

Keers R, Aitchison KJ (2010) Gender differences in antidepressant drug response. Int Rev Psychiatr 22:485–500

Kelly DJ, Miellet S, Caldara R (2010) Culture shapes eye movements for visually homogeneous objects. Front Psychol 1:6

Laeng B, Sirois S, Gredeback G (2012) Pupillometry: a window to the preconscious? Perspect Psychol Sci 7:18–27

Laretzaki G, Plainis S, Vrettos I, Chrisoulakis A, Pallikaris I, Bitsios P (2011) Threat and trait anxiety affect stability of gaze fixation. Biol Psychol 86:330–336

Malcolm GL, Lanyon LJ, Fugard AJB, Barton JJS (2008) Scan patterns during the processing of facial expression versus identity: an exploration of task-driven and stimulus-driven effects. J Vision 8:2.1–9

Perlman SB, Morris JP, Wyk BCV, Green SR, Doyle JL, Pelphrey KA (2009) Individual differences in personality predict how people look at faces. Plos One 4: doi:10.1371/Journal.Pone.0005952

Simonsen A, Scheel-Kruger J, Jensen M, Roepstorff A, Moller A, Frith CD, Campbell-Meiklejohn D (2014) Serotoninergic effects on judgments and social learning of trustworthiness. Psychopharmacology. doi:10.1007/s00213-014-3444-2

Stahl SM (2010) Enhancing outcomes from major depression: using antidepressant combination therapies with multifunctional pharmacologic mechanisms from the initiation of treatment. CNS Spectrums 15:79–94

Walker-Smith GJ, Gale AG, Findlay JM (2013) Eye movement strategies involved in face perception. Perception 42:1120–1133

Wells TT, Clerkin EM, Ellis AJ, Beevers CG (2014) Effect of antidepressant medication use on emotional information processing in major depression. Am J Psychiatry 171:195–200

Whalen PJ, Kagan J, Cook RG, Davis FC, Kim H, Polis S, McLaren DG, Somerville LH, McLean AA, Maxwell JS, Johnstone T (2004) Human amygdala responsivity to masked fearful eye whites. Science 306:2061–2061