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Title:
Acute caffeine ingestion affects surround suppression of perceived contrast

Date:
2018-01-01

Citation:
Nguyen, B. N., Hew, S. A., Ly, J., Shin, H. Y., Wong, J. C., Yeung, E. & McKendrick, A. M. (2018). Acute caffeine ingestion affects surround suppression of perceived contrast. Journal of Psychopharmacology, 32 (1), pp.81-88. https://doi.org/10.1177/0269881117725684.

1. Article type: Original paper

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3. Title (max 50 words): Acute caffeine ingestion affects surround suppression of perceived contrast

Running head (max 50 characters): Caffeine affects perceptual surround suppression

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5. Abstract: (247 words)

Caffeine is a widely used psychostimulant that is associated with increased acetylcholine levels in mammalian brain and acetycholinesterase antagonism. Acetylcholine, a neuromodulator, plays an important role in the processing of visual information. One key example in human vision thought to at least partly involve cholinergic neuromodulation is perceptual surround suppression of contrast, whereby the perceived contrast of a pattern is altered by the presence of a neighbouring

pattern. Perceptual surround suppression is weaker with pharmacological administration of donepezil (a centrally-acting acetylcholine enzyme inhibitor) in healthy human observers. Here, we test whether temporarily manipulating caffeine levels (from complete washout to a controlled dose of caffeine) has a similar effect on perceptual surround suppression in 21 healthy young adults (aged 20-24, 11 females). Neither ingestion of a caffeine pill nor placebo altered contrast judgments when the target pattern was presented on a uniform grey background ($p=0.54$). With caffeine ingestion, perceptual surround suppression strength was reduced relative to baseline (prior to pill ingestion, $p=0.003$) and placebo ($p=0.029$), irrespective of whether the surround was oriented parallel or orthogonal to the central target. While daily habitual caffeine consumption of low-to-moderate doses (<400 mg/day, estimated from a written questionnaire) is not predictive of performance, our study indicates that acute consumption of caffeine on the day of testing influences perceptual surround suppression strength. Perceptual surround suppression is predominantly attributed to inhibitory processes involving the major cortical inhibitory neurotransmitter, GABA. Our results point to the involvement of other neuromodulators, possibly cholinergic, in perceptual surround suppression.

Clinical trials registration: This trial is registered in the Australian New Zealand Clinical Trials Registry (www.ANZCTR.org.au/ACTRN12616000423415p.aspx, Trial ID: #12616000423415).

Keywords: caffeine, acetylcholine, surround suppression, vision, visual perception

Number of figures: 4

Number of tables: 0

Number of words: 4397 words (main text)

Introduction

Caffeine is the most widely consumed psychoactive substance. In addition to its well-known stimulant effects via adenosine receptor blockade in the brain (Fredholm et al., 1999; Ribeiro and Sebastiao, 2010), caffeine can influence neurotransmission, including effects on the cholinergic (Pohanka, 2014), dopaminergic (Garrett and Griffiths, 1997), noradrenergic (Berkowitz et al., 1970), and serotonergic (Berkowitz and Spector, 1971) pathways. Acetylcholine is a neuromodulator that is implicated in visual sensory processing. A well-studied visual perceptual phenomenon that is thought to at least partially involve acetylcholine (Kosovicheva et al., 2012) is surround suppression of contrast. Surround suppression of contrast describes the phenomena where the apparent contrast of a visual stimulus can be markedly affected by its surrounding context. Typically, the apparent contrast of a target (e.g. a striped grating pattern) is reduced when surrounded by a pattern of higher contrast, compared to when viewed in isolation (Cannon and Fullenkamp, 1991; Chubb et al., 1989; Ejima and Takahashi, 1985). The strength of such perceptual suppression depends on a range of stimulus characteristics, such as the contrast (Ejima and Takahashi, 1985; Xing and Heeger, 2001) and orientation (Cavanaugh et al., 2002; Levitt and Lund, 1997; Xing and Heeger, 2000) of the neighbouring stimulus (the surround) relative to the central target. Perceptual surround suppressive effects show strong quantitative agreement

65 with responses measured from human primary visual cortex (V1) using fMRI (Zenger-
66 Landolt and Heeger, 2003; Haynes et al., 2003; Williams et al., 2003; Pilhaja et al.,
67 2008; Joo et al., 2012), which suggests V1 as the earliest cortical area with the
68 neuronal architecture capable of mediating perceptual surround suppressive effects in
69 humans. Convergent evidence from primate work also points to a complex interaction
70 between intra-V1, feedforward and feedback connections to V1 as contributing to
71 visual surround suppression (Angelucci and Bressloff, 2006).
72
73 A recent study demonstrated that ingestion of the centrally-acting acetylcholine
74 enzyme inhibitor, donepezil (Kosasa et al., 1999; Rogers et al., 1991), reduces
75 perceptual surround suppression of contrast in healthy adults (Kosovicheva et al.,
76 2012). An alternate method for manipulating acetylcholine levels may be caffeine
77 ingestion. Caffeine administration enhances acetylcholine release in the hippocampus
78 of awake, freely moving rats (Carter et al., 1995) and in stimulated cerebral cortex
79 slices of rats naïve to caffeine (Corradetti et al., 1986). In addition, caffeine shows
80 antagonistic effects on human acetylcholinesterase samples (Pohanka and Dobes,
81 2013). There is also convergent evidence from human behavioural work supporting a
82 role for caffeine in influencing the cholinergic system. Scopolamine is an anti-
83 cholinergic drug that adversely affects performance on cognition tests. Riedel et al

84 (1995) demonstrated that scopolamine-induced deficits in short-term memory could
85 be attenuated by acute consumption of caffeine, suggesting that caffeine has
86 cognition-enhancing properties by acting, at least partly, through cholinergic
87 pathways. If caffeine has cholinergic effects and potentially increases acetylcholine
88 levels in the human brain, its ingestion may influence the strength of perceptual
89 surround suppression of contrast.
90
91 In this study, we test the hypothesis that acute caffeine ingestion in healthy observers
92 affects perceptual surround suppression of contrast by using a common task that is
93 often used to investigate spatial contextual interactions in human vision (Zenger-
94 Landolt and Heeger, 2003; Yoon et al., 2009; Yoon et al., 2010; Kosovicheva et al.,
95 2012). We predicted that perceptual surround suppression strength would decrease
96 following caffeine consumption (similar to the effects of donepezil). We presented
97 surround grating patterns that were oriented parallel and orthogonal to the target
98 pattern to determine whether the effect of caffeine on perceptual suppression was
99 orientation-dependent, as there are both orientation specific and non-specific aspects
100 of perceptual surround suppression (Schallmo and Murray, 2016). If caffeine acts via a
101 similar mechanism as donepezil to influence contrast perception, we hypothesise that
102 the reduction in perceptual surround suppression following caffeine would only be

present for the parallel surround condition, as previously reported by Kosovicheva et al (2012).

Methods

Participants

Experimental procedures were approved by the Human Research Ethics Committee of the University of Melbourne (ID #1646382) and complied with the tenets of the Declaration of Helsinki. Written informed consent was obtained prior to testing. Our research hypothesis was based on a previous study (Kosovicheva et al., 2012) that measured the effect of donepezil on surround suppression of perceived contrast in a group of 19 healthy, young observers (mean age 26 years), compared to a placebo pill. In that study, a paired t-test (drug vs placebo) found a significant difference in performance (group mean difference=1% contrast, standard deviation=1.3% contrast) with 90% power (alpha=0.05, 2-tailed), rejecting the null hypothesis that the mean difference was 0% contrast. We aimed for a similar number of participants in our sample to be able to detect a comparable difference in perceptual surround suppression with and without acute caffeine ingestion. The final sample size was 21 young adults (aged 20-24, 11 females). All participants were screened to ensure visual acuity of 6/7.5 or better in each eye with habitual refractive correction, and no

systemic conditions (e.g. diabetes, epilepsy) or medications (e.g. antidepressants) known to affect visual function.

Caffeine questionnaire

Participants completed a questionnaire modified from Modi et al. (2010) to evaluate caffeine intake over the past month. Participants indicated the frequency of consumption of food, beverages, and medications containing caffeine. Estimates of daily caffeine intake (mg/kg/day) were calculated based on the caffeine content (mg) per standard unit of consumption (see Table 1 from Modi et al., 2010) and normalised to the participant's weight (kg).

Experimental design

The experiment was a double-blind, placebo-controlled, randomised cross-over design. Participants attended two test sessions of up to 90 minutes each. As per previous studies (Haskell et al., 2005; Colzato et al., 2005), participants refrained from consuming caffeine for 24 hours prior to a test visit. A 12-hour caffeine washout period is sufficient to reduce salivary caffeine levels to negligible levels (< 1mg/mL) in habitual and non-habitual caffeine consumers (Haskell et al., 2005).

141 The first visit included the vision screening and caffeine questionnaire. At each visit,
142 participants completed pre-drug baseline visual perceptual tests (described in the next
143 section) and then consumed one of two types of pills with water:
144
145 (1) Caffeine (200 mg): 2 x 'No Doz Plus' tablets (Key Pharmaceuticals, Macquarie
146 Park, Australia). Each tablet consists of 100 mg caffeine, 10 mg Vitamin B1, and
147 10 mg Vitamin B3.
148 (2) Placebo (200 mg): 2 x 'Betamin' tablets (Sanofi-Aventis, Macquarie Park,
149 Australia). Each tablet consists of 100 mg Vitamin B1.
150
151 The pills were white, uncoated, round tablets of approximately the same size with no
152 engravings. The caffeine dosage (200 mg) was exactly 2 tablets and was chosen
153 because a comparable amount of oral caffeine (250 mg) elicits changes in the blood-
154 oxygen dependent magnetic resonance imaging (MRI) signal from the visual cortex in
155 healthy adults (Laurienti et al., 2002). Doses of 250 mg caffeine have also yielded
156 measurable changes on a visual feature binding task in healthy young adults (Colzato
157 et al., 2005). The magnitude and timing of peak plasma caffeine levels following oral
158 caffeine ingestion varies considerably amongst individuals (Fredholm et al., 1999;
159 Robertson et al., 1978). Nevertheless, we constrained the visual perceptual testing to

occur within a specified time frame based on previous measures of the approximate time when an absolute dose of 250 mg caffeine reaches its peak plasma concentration in the majority (89%) of healthy young individuals (Robertson et al., 1978). Hence, participants waited between 30-60 minutes, during which time participants waited quietly in the testing room, before repeating the visual perceptual tests. No other tasks were completed during the test session. The order of pill administration was randomised and prepared by author BNN who was neither tested nor conducted participant testing, so that all other investigators and participants were blinded. The second session was scheduled at least 2 days after the first to ensure caffeine washout.

Visual tasks

Participants were refractively corrected for near binocular viewing (40 cm). Gamma-corrected stimuli were generated off-line in Matlab R2013b (Mathworks, Natick, MA, USA) and presented on an iPad-3 tablet device (Apple Inc., Cupertino, CA, United States; frame rate: 60 Hz; screen resolution: 2048 × 1536 pixels) using the open-access platform 'Psypad' (Turpin et al., 2014). The Psypad app selects which stimulus image to display from the pre-generated library of images according to a customisable staircase procedure. The image library and staircase configuration used for this study can be downloaded from the Psypad server (http://server.psypad.net.au). An example test

179 ('Annular centre-surround task: which quadrant is the odd one out?') can be viewed in
180 Psypad Demo mode.
181
182 Stimuli were drawn as per Kosovicheva et al (2012), except that the stimulus size was
183 scaled (reduced to 0.8 of the original size used by Kosovicheva et al 2012) to fit the
184 iPad screen at the working distance (40 cm). A central black fixation point was
185 provided. The image background was set to mean luminance (172 cd/m^2 for an iPad at
186 constant maximum brightness). Three surround conditions were tested: (1) No
187 surround (2) Parallel surround (3) Orthogonal surround. For the 'no surround'
188 condition, an annulus (inner radius: 2.5°, outer radius: 5°) was presented in the centre
189 of the screen, consisting of a vertical sinusoidal grating (1.1 cycles/degree, 20%
190 contrast) divided into four quadrants (Figure 1A). One quadrant was randomly chosen
191 to be of variable contrast. The stimulus appeared for 200 ms to minimise saccadic eye
192 movements. Participants chose the odd quadrant out (four-alternative forced choice,
193 4AFC). For the remaining conditions (Figures 1B and 1C) the task was the same, except
194 that the annulus was surrounded by sinusoidal gratings of the same spatial frequency
195 and phase extending from 0-2.5° radius and from 5-10° radius (80% contrast).
196

Increment detection thresholds (relative to 20% reference contrast) were measured for each quadrant using four interleaved 2-down 1-up staircases of four reversals (step sizes: 4%, 2%, 1%, 1%), and were repeated twice. The staircases began at a supra-threshold increment level (20% contrast increment for no surround, 40% contrast increment for surround conditions). Thresholds were estimated at approximately the 70% probability of seeing (Wetherill and Levitt, 1965). The final threshold was the average of the final two reversals of the two repeats, averaged across all four quadrants.

The no surround condition was always tested first for training purposes, and because performance on this baseline task does not vary considerably among individuals. The remaining tasks were randomised, with half the group performing the parallel surround condition first (and vice versa) to balance for learning and/or fatigue effects. The visual perceptual tests took approximately 15 minutes, in addition to practice runs and rest breaks between trials.

Statistical analysis

SPSS V22.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Data were tested for normality (Kolmogorov-Smirnov test) and compared using a repeated

measures analysis of variance (RM-ANOVA). Huynh-Feldt adjustments were made for non-spherical data. To compare the strength of suppression, a 'suppression index' was calculated (surround threshold/no surround threshold). A ratio of 1 indicates no effect of the surround. An index >1 indicates suppression, i.e. compared to having no surround, a larger contrast increment was required to reliably detect the odd quadrant. Cohen's *d* effect sizes were calculated to measure the change in suppression from baseline after caffeine ingestion, where effect sizes of d = 0.2, 0.5, 0.8 were considered small, medium, and large effects, respectively (Cohen, 2013). For all comparisons, $p < 0.05$ was considered statistically significant.

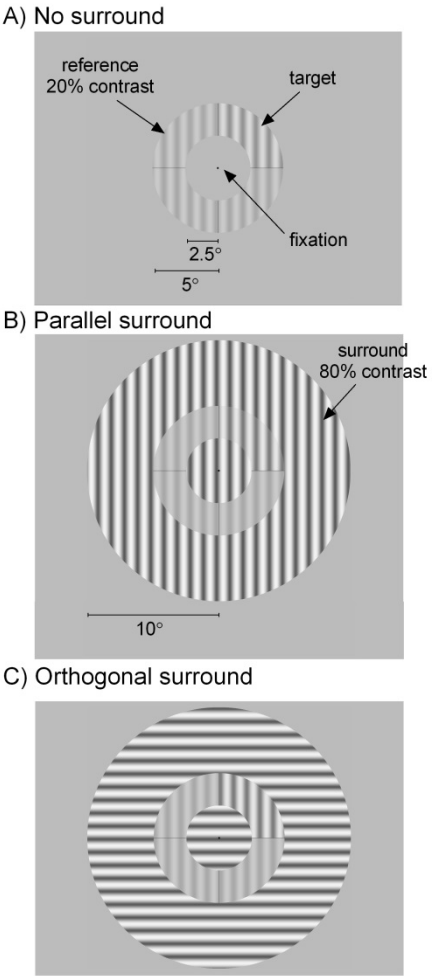


Figure 1. Example stimuli used to measure perceptual surround suppression. Contrast increment detection thresholds were measured for three surround conditions: (A) No surround (B) Parallel surround (C) Orthogonal surround. Participants chose which of the four quadrants was the odd one out (the 'target') relative to the rest of the annulus (20% reference contrast). The surround was 80% contrast. In these examples, the top-right hand quadrant of the central annulus is the odd one out.

Results

All participants completed the testing and were asked to guess which pill had been consumed at each of the two visits. The proportion of correct responses (62%, 13 of 21 participants) was not significantly different from chance (50% guess rate; chi-square test of proportions: p=0.44), indicating a successful blinding procedure. The median wait time between pill ingestion and repeat visual perceptual testing was 35 minutes for caffeine (range: 30-56 minutes) and 33 minutes for placebo (range: 30-52 minutes). The distribution of time post-pill ingestion was the same for the two interventions (Kolmogorov-Smirnov test: p=0.59).

Baseline contrast increment thresholds

We first considered whether baseline performance prior to pill ingestion varied systematically across the two visits. Overall, thresholds were not significantly different at the two visits (RM-ANOVA main effect of visit: $F(1,20)=0.55$, $p=0.47$, $\eta_p^2=0.03$), but were different for the three surround conditions (main effect of surround: $F(2,40)=63.11$, $p<0.0001$, $\eta_p^2=0.76$). There was no interaction between visit and surround condition ($F(2,40)=0.35$, $p=0.71$, $\eta_p^2=0.02$), indicating that performance on all tasks was similar across test sessions. Hence, baseline data were pooled across both visits for subsequent comparisons. Consistent with previous literature in healthy

observers (Kosovicheva et al., 2012; Yu and Levi, 2000; Xing and Heeger, 2000; Cannon and Fullenkamp, 1991), contrast increment thresholds were higher for the parallel (mean ± standard deviation: 13.31% ± 4.32%) than orthogonal condition (10.38% ± 3.06%), relative to the no surround condition (4.74% ± 1.10%), demonstrating the expected pattern of orientation-dependent surround suppression prior to any intervention.

Effect of interventions on the no surround condition

Our measure of surround suppression strength (suppression index) depends on performance on the no surround condition. We therefore determined whether the pills (caffeine versus placebo) had an effect on the no surround condition. No effect of intervention was found when baseline contrast increment thresholds (average of 2 visits) were compared with the thresholds observed following ingestion of caffeine and placebo (Figure 2, main effect of intervention: $F(2,40)=0.63$, $p=0.54$, $\eta_p^2=0.03$).

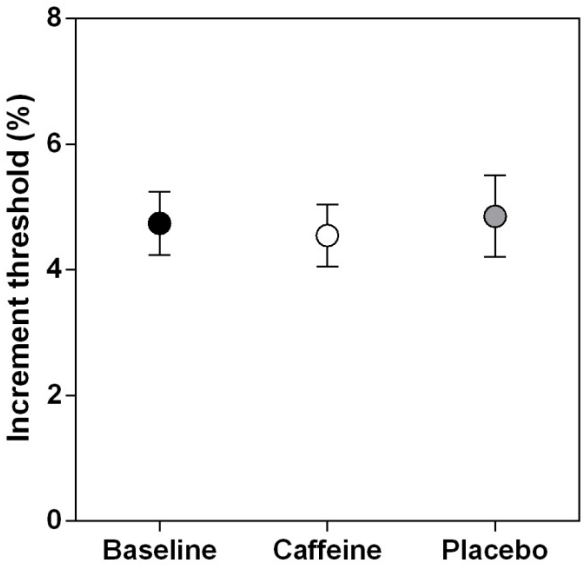
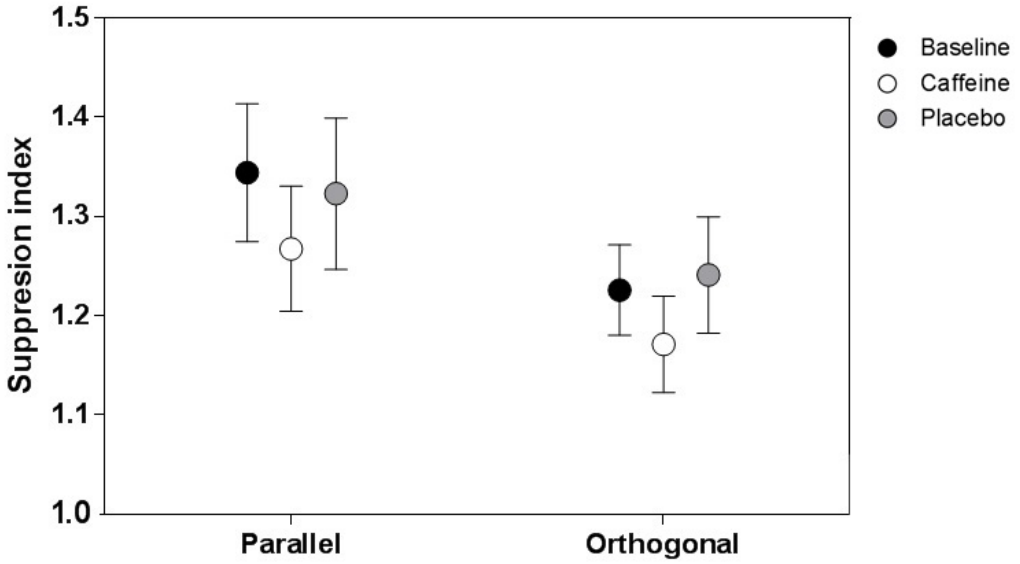


Figure 2. Mean contrast increment detection thresholds for the no surround condition following different interventions (baseline, caffeine, placebo). Error bars are the 95% confidence intervals of the mean.

Effect of intervention on surround suppression strength

We found a main effect of intervention on surround suppression strength (Figure 3; Huynh-Feldt ε=0.80, F(1.59,31.82)=8.79, p=0.002, η_p^2=0.31). After taking the caffeine pills, suppression strength was reduced for both parallel (Cohen's *d*=0.53) and orthogonal (*d*=0.54) surround conditions relative to baseline (Bonferroni pairwise comparisons: p=0.003) and placebo (p=0.029). There was no difference in suppression index between placebo and baseline (p>0.05), indicating that only caffeine, and not the vitamin pill, altered visual performance.

Figure 4 plots the 'effect of caffeine' as the difference in suppression between having no caffeine (average of placebo and baseline) and having caffeine. The reduction in surround suppression strength following caffeine ingestion was similar for parallel and orthogonal surrounds (intervention x surround interaction: Huynh-Feldt ε=0.69, F(1.39,27.70)=0.38, p=0.61, η_p^2=0.02).



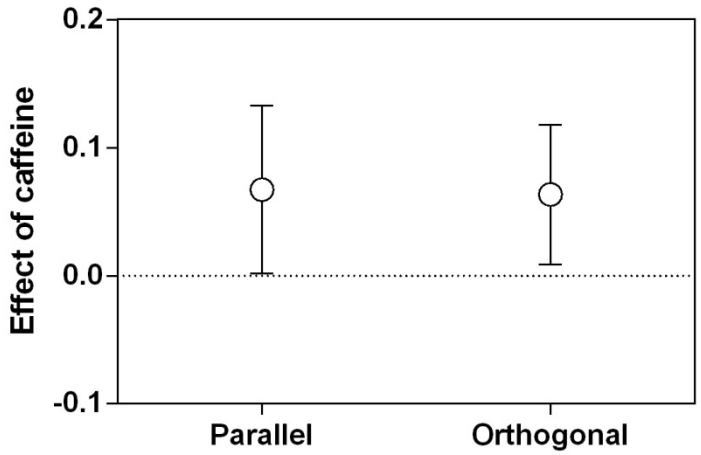
284

285 **Figure 3.** Effect of intervention (baseline, placebo or caffeine) on suppression index. A

286 suppression index of 1 indicates no effect of the surround; an index >1 indicates

287 surround suppression. Error bars are the 95% confidence intervals of the mean.

288



289

290 **Figure 4.** Mean effect of caffeine (difference between having no caffeine versus having
291 caffeine) on suppression index. The average difference was above 0 (horizontal dotted
292 line) regardless of surround condition, indicating that caffeine ingestion reduced
293 suppression relative to baseline and placebo. Error bars are the 95% confidence
294 intervals of the mean.

295

Relationship to habitual caffeine consumption

Estimates of daily caffeine intake normalised to an individual's weight (mg/kg/day) ranged from 0.15 to 6.26 mg/kg/day (median = 1.57 mg/kg/day). The highest habitual caffeine consumption observed in our cohort was 356 mg/day, which is slightly more than 2.5 cups of coffee per day. Hence, the range of habitual caffeine consumption in this study was low to moderate only. There was no relationship between the effect of caffeine on suppression index and daily caffeine intake estimates (Pearson correlation analysis: parallel r=-0.18, p=0.44; orthogonal r=-0.10, p=0.65). This implies that after caffeine washout (in this case, 24 hours), acute caffeine consumption affects perceptual surround suppression independent of a person's reported routine caffeine consumption.

Discussion

We found that visual perceptual surround suppression was altered relative to baseline after a controlled dose of caffeine. Visual surround suppression tasks are considered perceptual analogues of neuronal centre-surround suppression in visual cortex, because stimulus properties (e.g. orientation, contrast) similarly influence human perception and primate visual cortical neural responses (Cannon and Fullenkamp, 1991; Chubb et al., 1989; Shushruth et al., 2013; Xing and Heeger, 2000; Yu et al.,

315 2001). Numerous studies have measured perceptual surround suppression to
316 investigate proposed alterations in neuronal mechanisms underlying the healthy
317 ageing process (Karas and McKendrick, 2009; Karas and McKendrick, 2012), migraine
318 (Battista et al., 2011), Alzheimer's disease (Zhuang et al., 2016), schizophrenia (Dakin
319 et al., 2005; Yoon et al., 2009), depression (Golomb et al., 2009), and bipolar disorder
320 (Schallmo et al., 2015). Perceptual surround suppression has even been considered a
321 potential translational tool for use in clinical trials for schizophrenia (Barch et al., 2012;
322 Gold et al., 2012). Although the average effect of caffeine relative to baseline
323 performance is small (mean 0.07 difference in suppression index, see Figure 4),
324 average group differences between control and clinical populations in perceptual
325 surround suppression strength vary approximately from 0.14-0.15 in migraine (Battista
326 et al., 2011), Alzheimer's (Zhuang et al., 2017), depression (Golomb et al., 2009) and
327 bipolar disorder (Schallmo et al., 2015) to 0.35-0.4 in schizophrenia (Yoon et al., 2009)
328 and healthy ageing (Karas and McKendrick 2012). Our small but statistically significant
329 effect of caffeine constitutes between 17-48% of previously reported average group
330 differences in perceptual surround suppression. Our findings therefore have far-
331 reaching implications for the interpretation of research findings. Peak concentration of
332 oral caffeine occurs within 30-60 minutes (Fredholm et al., 1999; Robertson et al.,
333 1978), half of which remains in the body 4-5 hours after initial ingestion (Blanchard

334 and Sawers, 1983; Cook et al., 1976). Thus, any caffeine consumed by a participant
335 could still be present at significant plasma concentrations hours later on the same day.
336 We demonstrate that oral caffeine ingestion can affect perceptual tests of surround
337 suppression in as little as 30 minutes, suggesting that caffeine levels may need to be
338 controlled for future experimental work.
339
340 Facilitatory effects on mood, vigilance, and performance on psychomotor and
341 cognitive tasks following acute caffeine ingestion are well-documented (Smit and
342 Rogers, 2000; Haskell et al., 2005; Attwood et al., 2007; Adan and Serra-Grabulosa,
343 2010), and are attributed to caffeine's antagonistic action at the level of adenosine
344 receptors in the central nervous system (Fredholm et al., 1999; Ribeiro and Sebastiao,
345 2010). Caffeine also influences the formation and release of a variety of
346 neurotransmitters that are implicated in cognition, including noradrenaline, serotonin,
347 acetylcholine, and dopamine (reviewed by Nehlig et al., 1992). In our case, improved
348 vigilance or attention does not readily explain the reduction in perceptual surround
349 suppression of contrast because increment contrast detection thresholds for the no
350 surround condition were unaffected by caffeine ingestion (see Figure 2). Nevertheless,
351 given caffeine's ability to modulate activation of cortical areas related to attention
352 (Serra-Grabulosa et al., 2010), it is worth considering whether attention may be a

353 contributing factor in our study. A specific form of visual spatial attention, 'feature-
354 based' attention, has recently been shown to modulate human perceptual surround
355 suppression (Flevaris and Murray, 2015a, 2015b), which requires an observer to attend
356 to a particular feature or stimulus attribute (e.g. orientation) that is present in both the
357 centre (target) and surround pattern. If attention is directed to a stimulus feature that
358 is the same for the centre and surround, perceptual surround suppression is enhanced
359 relative to when the stimulus feature does not match. Our visual stimuli had fixed
360 spatial frequency, contrast, size, and phase, with the only difference between centre
361 and surround being the orientation (in order to test the orientation-specificity of the
362 effect of caffeine). To comment on whether caffeine may have influenced attention,
363 and specifically 'feature-based' visual spatial attention, would require a different
364 experimental design where more than one stimulus feature is altered. Moreover,
365 although attention was not explicitly controlled in the present study, spatial attention
366 was evenly distributed across our visual stimuli – on any given trial, the odd quadrant
367 was randomly chosen, and so observers did not benefit from focusing their attention
368 to only one part of their field of view.
369
370 We also considered whether our results might be dependent on habitual caffeine
371 consumption. On the one hand, tolerance to the effects of caffeine (e.g. on mood,

372 sleep disruption, cardiovascular effects) develops quickly in a matter of days with
373 frequent caffeine consumption (Fredholm et al., 1999). On the other hand, while some
374 studies find that high caffeine consumers are more likely than low-moderate
375 consumers to experience positive effects of caffeine on certain cognitive tasks that
376 measure speed of processing and reaction time (Attwood et al., 2007; Smit and Rogers,
377 2000), there are also reports showing improved cognitive performance on attention
378 and working memory tasks and self-rated alertness following caffeine consumption,
379 irrespective of caffeine habit (Haskell et al., 2005, Rogers et al., 2003).. We found no
380 correlation between daily caffeine intake levels and the effect of caffeine on visual
381 perceptual surround suppression, implying that acute caffeine consumption similarly
382 influences visual performance on this specific task in habitual and infrequent caffeine
383 consumers.
384
385 The estimates of daily caffeine intake reported in this study varied from 0.15 to 6.26
386 mg/kg/day, or 10 to 356 mg/day. This range reflects the full spectrum of typical dietary
387 caffeine consumption in healthy adults aged 19-30 years (10-90th percentile = 24-330
388 mg/day, data from the United States National Health and Nutrition Examination Survey
389 2001-2010, see (Fulgoni et al., 2015). The inclusion of participants with very low
390 caffeine consumption (0-50 mg/day, 24% of participants) is also a strength of this

391 study, as non-consumers of caffeine are notably rare (Haskell et al., 2005).
392 Furthermore, we considered caffeine intake from multiple sources, which better
393 reflects normal human consumption, as opposed to studies that have only considered
394 caffeine content in beverages (e.g. see Mitchell et al 2014). A possible limitation of our
395 experiments is that we did not tightly control for the time of day of the experiments.
396 Previous research has shown that the effect of caffeine on somnolence (sleepiness)
397 and subjective mood is influenced by an interaction between circadian typology and
398 time of day (Adan et al., 2008). Alertness and mood are not known contributing factors
399 to our visual perceptual measures. All of our participants were tested between 11am
400 and 6pm; however, tight control on the visit timing between the first and second
401 session for a given individual was not enforced. Time of day did not influence the
402 effect of caffeine on our primary outcome measure (change in suppression index from
403 baseline to post-caffeine pill, results not shown). Nevertheless, ensuring that the
404 placebo and caffeine sessions are conducted at the same time of day for each
405 individual would likely decrease noise in the data, and should be considered for future
406 studies.
407
408 We observed visual perceptual changes after only a moderate dose of caffeine (200
409 mg), which was chosen to be comparable to previous work in healthy young adults

410 reporting changes in visual cortical responses with MRI (Laurienti et al., 2002) and
411 visual perceptual feature binding (Colzato et al., 2005) with caffeine. Other studies
412 have opted for higher doses (400 mg) of caffeine to produce robust effects (not seen
413 with 250 mg) in improving mood and cognitive performance (e.g. see Attwood et al
414 2007). Oral administration of caffeine increases extracellular levels of cortical
415 acetylcholine in awake rats in a dose-dependent manner (Carter et al., 1995). Whether
416 the visual perceptual changes observed here with acute caffeine consumption are
417 similarly dose-dependent is unknown and requires further controlled testing with
418 caffeine doses that are tailored to a person's weight. Furthermore, given the wide
419 range of individual factors that may interact with caffeine (e.g. use of alcohol, illicit
420 drugs, oral contraceptives, anticonvulsant drugs, and smoking), it would be necessary
421 to measure the pharmacokinetics of caffeine in a given individual over an extended
422 period of time (e.g. 6 hours).
423
424 In this study, caffeine equally influenced perceptual suppression in the presence of
425 parallel and orthogonal surround stimuli, unlike donepezil's effect that is specific to
426 parallel surround stimuli (Kosovicheva et al., 2012). Several distinct neural mechanisms
427 are considered to contribute to perceptual surround suppression: one that is
428 orientation specific, and another that is non-orientation specific (Schallmo and Murray,

2016). Our findings suggest that caffeine's predominant effect is on the non-orientation specific aspect of perceptual surround suppression. Our motivation for this study arose from caffeine's purported effect of increasing cortical acetylcholine. We chose to focus particularly on the cholinergic system because suppression of perceived contrast is a spatial contextual phenomenon, and systemic cholinergic enhancement with donepezil has been shown to influence the spatial spread of human fMRI responses from early visual areas – particularly V1 (Silver et al., 2008), which is believed to be the neural locus of perceptual suppression of contrast (Zenger-Landolt and Heeger, 2003; Haynes et al., 2003; Williams et al., 2003; Pilhaja et al., 2008; Joo et al., 2012). Further support for primarily considering the cholinergic system comes from a more recent study by Gratton et al (2017) investigating visual spatial perception in healthy human observers. In that study, high-contrast flanking distractors were used to produce a perceptual suppressive effect by reducing an observer's ability to detect a difference in contrast (in this case, a contrast decrement) of a peripherally placed target (3° eccentricity). Pharmacological cholinergic enhancement with donepezil improved detection of the contrast target, but no such effects were seen with dopaminergic or noradrenergic enhancement (Gratton et al., 2017). We found a similar facilitatory effect on the spatial suppression of perceived contrast after caffeine ingestion, which we attribute to a likely enhancement of the cholinergic, rather than

448 noradrenergic or dopaminergic, pathway. However, acetylcholine does not operate in
449 isolation, but influences other neuromodulator levels. For example, in rodent cortex,
450 stimulation of muscarinic cholinergic receptors inhibits the release of gamma-
451 aminobutyric acid (GABA) (Sugita et al., 1991), a key inhibitory neuromodulator
452 involved in perceptual surround suppression (Yoon et al., 2010). Furthermore,
453 application of acetylcholine to visual cortical neurones in marmoset monkeys broadens
454 their orientation tuning – an effect that is attributed to reduced GABA-ergic inhibition
455 (Zinke et al., 2006). Hence, it is possible that our observed effects result from a
456 complex cascade of altered neuromodulation, which either only acts on the non-
457 oriented component of suppression, or alternately reduces the orientation specificity
458 of the effect. Future work investigating the effect of caffeine on visual perception
459 could incorporate human neuroimaging methods that enable *in vivo* measurement of
460 brain metabolites such as GABA (Yoon et al., 2010) to test this idea more directly.
461
462 **Conclusions**
463 We show that caffeine affects visual perceptual surround suppression of contrast. The
464 effect is present 30-60 minutes after ingestion of a commercially available caffeine pill
465 (i.e. an absolute, moderate 200 mg dose of caffeine), following a period of caffeine
466 washout (24 hours). Firstly, this finding has practical implications on studies utilising

such visual behavioural methods to indirectly investigate centre-surround interactions in a range of human conditions. Secondly, although the exact biological mechanism of action of caffeine contributing to the visual perceptual changes observed here is yet unknown and falls outside the scope of our experimental design, this study provides evidence from human behavioural work to further understand the mechanisms underlying perceptual surround suppression. Perceptual surround suppression is predominantly attributed to the major cortical inhibitory neurotransmitter, GABA. In this study, we considered the potential for caffeine to exert modulatory effects on cholinergic pathways, and more recent evidence for visual perceptual facilitatory effects from cholinergic (and not noradrenergic or dopaminergic) enhancement. Our results point to the involvement of other neuromodulators, possibly cholinergic, in perceptual surround suppression. Further work is necessary to elucidate the mechanism/s of caffeine (e.g. directly via muscarinic cholinergic enhancement or indirectly via reduction in GABA), that impact on visual perception.

6. Acknowledgements: The authors wish to thank the participants who volunteered for the study.

7. Funding: This work was supported by an Australian Research Council Discovery Project Grant (#DP140100157) to author AMM.

8. Declaration of conflicting interests: The authors declare that there is no conflict of interest.

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