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Genetic variation in brain-derived neurotrophic factor and human fear conditioning

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Abstract

Brain-derived neurotrophic factor (BDNF) has been implicated in hippocampal-dependent learning processes, and carriers of the Met allele of the Val66Met *BDNF* genotype are characterized by reduced hippocampal structure and function. Recent nonhuman animal work suggests that BDNF is also crucial for amygdala-dependent associative learning. The present study sought to examine fear conditioning as a function of the *BDNF* polymorphism. Fifty-seven participants were genotyped for the *BDNF* polymorphism and took part in a differential-conditioning paradigm. Participants were shocked following a particular conditioned stimulus (CS +) and were also presented with stimuli that ranged in perceptual similarity to the CS+ (20, 40 or 60% smaller or larger than the CS+). The eye blink component of the startle response was measured to quantify fear conditioning; post-task shock likelihood ratings for each stimulus were also obtained. All participants reported that shock likelihood varied with perceptual similarity to the CS+ and showed potentiated startle in response to CS ± 20% stimuli. However, only the Val/Val group had potentiated startle responses to the CS+. Met allele carrying individuals were characterized by deficient fear conditioning – evidenced by an attenuated startle response to CS+ stimuli. Variation in the *BDNF* genotype appears related to abnormal fear conditioning, consistent with nonhuman animal work on the importance of BDNF in amygdala-dependent associative learning. The relation between genetic variation in *BDNF* and amygdala-dependent associative learning deficits is discussed in terms of potential mechanisms of risk for psychopathology.

Keywords

Anxiety; BDNF; fear; fear-potentiated startle; generalization; startle

A common single nucleotide polymorphism (SNP) in the human brain-derived neurotrophic factor (*BDNF*) gene has been identified that produces a functional valine (Val) to methionine (Met) substitution in the prodomain at codon 66 (Val66Met; Egan *et al*. 2003). The heterozygous Val/Met genotype occurs in approximately 20–30% of Caucasian

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populations; the Met/Met allele is much more infrequent (about 2–3%; Shimizu *et al.* 2004). Met substitution reduces BDNF trafficking and activity-dependent secretion (Chen *et al.* 2004; Egan *et al.* 2003). Consistent with the role of BDNF in hippocampal-dependent cognitive function in nonhuman animals (Figurov *et al.* 1996; Korte *et al.* 1995; Lu & Gottschalk 2000; Patterson *et al.* 1996; Poo 2001), individuals who carry a Met allele of the *BDNF* polymorphism have relatively poor memory, as well as reduced hippocampal activation during memory tasks, compared with individuals homozygous for the Val allele (Dempster *et al.* 2005; Egan *et al.* 2003; Hariri *et al.* 2003).

Recent work highlights the role of BDNF in other forms of associative learning, including amygdala-dependent fear conditioning (Monfils *et al.* 2007; Rattiner *et al.* 2005; Ressler & Davis 2003). BDNF is expressed in the amygdala during fear conditioning (Chhatwal *et al.* 2006; Conner *et al.* 1997; Jones *et al.* 2007; Yan *et al.* 1997) – and temporal patterns of BDNF expression in the basolateral amygdala suggest that BDNF is necessary for the acquisition of conditioned fear (Ou & Gean 2006; Rattiner *et al.* 2004a,b). Moreover, Chen *et al.* (2006) found that expression of a Met allele produced altered BDNF expression and increases in anxiety-related behaviors.

Fear conditioning in humans and nonhuman animals can be measured through potentiation of the startle response – a cross-species defensive reflex to an abrupt and intense stimulus (Davis 1984; Davis 2006; Grillon & Baas 2003). The startle response is larger when the eliciting stimulus is delivered in the presence of a cue previously paired with a shock – a phenomenon referred to as *fear-potentiated startle* (Brown *et al.* 1951; Davis 2006; Davis *et al.* 1993; Grillon & Baas 2003). Extensive neurobiological research in nonhuman animals has highlighted the central role of the amygdala during fear conditioning (Pare *et al.* 2004; Sigurdsson *et al.* 2007; Wilensky *et al.* 2006) and in the potentiation of the startle reflex (Davis 2006; Davis *et al.* 1993).

Consistent with this body of work, the human startle reflex is enhanced in the context of aversive stimuli and situations: startle magnitude is larger in the presence of conditioned stimuli (Grillon & Davis 1997) and in response to threat of shock (Grillon *et al.* 1991); moreover, startle magnitude tracks the association between conditioned and unconditioned stimuli across acquisition and extinction periods of fear conditioning (Vansteenwegen *et al.* 1998; Walker *et al.* 2002).

Both human and nonhuman research indicates that the startle response can be used to measure amygdala-dependent fear conditioning (LaBar *et al.* 1998; Phelps *et al.* 2001; Phillips & LeDoux 1992). In light of recent work highlighting the importance of BDNF during amygdala-dependent associative learning, the goal of the present study was to relate variation in the human *BDNF* genotype to the fear-potentiated startle response during a differential fear-conditioning paradigm in which stimuli varied in their perceptual similarity to the CS+.

Methods and materials

Participants and genotyping

Sixty-two college students (33 females) were genotyped for the Val66Met single nucleotide *BNDF* polymorphism (rs6265). [From the original sample of 62 participants, 3 (two females) were excluded because they did not produce quantifiable startle responses; another 2 (one female) were excluded because their sample did not yield adequate genetic material for genotyping. Three samples were initially selected as the expected genotypes (Val/Val, Val/Met and Met/Met) based on melt analyses and were confirmed by DNA sequencing. These samples were used on every polymerase chain reaction (PCR) plate for comparison.] All participants received course credit for participation. DNA was extracted from buccal cells using the Quick Extract DNA Extraction Solution (Epicentre Technologies, Madison, WI, USA). Genotype analysis was performed with high-resolution melt analysis. PCR was carried out in a 10-μl volume with forward (5′-TGGTCCTCATCCAACAGCTC-3′) and reverse (5′-CCCAAGGCAGGTTCAAGAG-3′) primers. Each amplification was overlaid with mineral oil and contained 2 μl of extracted buccal DNA, 0.25 μ_M of each primer and 1× Light Scanner Master Mix (Idaho Technology Inc., Salt Lake City, UT, USA). Reaction conditions began with a denaturation at 94°C for 2 min, followed by 40 cycles of 94°C for 30 seconds, 66.6°C for 30 seconds and 72°C for 30 seconds. Melt analysis was performed between 75 and 95°C (0.1°C/seconds) with a Light Scanner (Idaho Technology Inc.) and SNP status determined using the Small Amplicon Module. The average peaks for the Met/Met, Val/Met and Val/Val genotypes were obtained at 84.8, 84.5 and 85.3°C, respectively. One individual with each genotype was sequenced to confirm accuracy of the high-resolution melt analysis (data not shown).

Stimuli

To assess fear conditioning in the present study, a paradigm was employed in which participants were shocked following a specific CS+ but were presented with a range CS− stimuli that varied in perceptual similarity to the CS+. This design was employed to provide a richer representation of fearful responding to complex stimuli, more akin to real-world scenarios where danger and safety cues share perceptual similarities (cf. Lissek *et al.* 2008).

To this end, seven rectangles that were identical in height (56 pixels) but ranged from 112 to 448 pixels in width served as the stimuli and were presented in red against a white background on a 19-inch monitor set with a resolution of 1024 × 768 pixels. The middle-sized rectangle (218 pixels wide) was always the threat cue (CS+); six other stimuli differed by 20, 40 or 60% in width from the CS+ (hereafter CS+, CS ± 20%, CS ± 40% and CS ± 60%, respectively). At a viewing distance of 25 inches, each stimulus occupied approximately 1.5°of visual angle vertically and 4.0–15.0°of visual angle horizontally.

The startle probe was a 50-ms burst of white noise that was set to a volume of 105 dB and was delivered through headphones using a noise generator (Contact Precision Instruments, Cambridge, MA, USA). Electrical shocks were delivered to the participant's left tricep using an electrical stimulator (Contact Precision Instruments) that produced 60 Hz constant AC stimulation between 0 and 5 mA for 500 ms. All stimuli and psychophysiological responses

were presented and recorded using PSYLAB hardware and PSYLAB 8 software (Contact Precision Instruments).

Procedure

The shock intensity for each participant was determined on an individual basis – participants initially received a mild shock, which was raised based on participant feedback. Participants were asked to choose a level of shock that would be uncomfortable but manageable.

A habituation phase (four trials) without any shocks was used to elicit initial extreme startle responses. Next, the experimenter informed the participant that they would *always* be shocked following the presentation of the middle length rectangle (i.e. the CS+) and that they would *never* be shocked following the presentation of all other rectangles. The experimenter showed a trial that consisted of the CS+ followed by a shock.

The remainder of the experiment consisted of three blocks of 12 trials (12 CS+, 8 CS ± 20%, 8 CS ± 40% and 8 CS ± 60% trials in total). The order of stimulus presentation was random; 4 CS+ stimuli were presented in each block. Stimuli were presented for 8 seconds with a 10–12 seconds intertrial interval (ITI); startle probes were delivered on every trial 5–7 seconds following stimulus onset. Startle probes were also presented six times during random ITI periods to reduce the predictability of the startle probes.

Last, all participants completed a self-report rating of shock likelihood. Each rectangle was rated using a 5-point Likert-type scale that ranged from “certainly not shocked” (1) to “certainly shocked” (5); “unsure” was the midpoint (3).

Data recording, reduction and analysis

Startle-elicited electromyographic (EMG) activity was recorded using a PSYLAB Stand Alone Monitor Unit and Bio Amplifier (Contact Precision Instruments). Two Ag–AgCl electrodes were positioned approximately 25 mm apart over the orbicularis oculi muscle beneath the left eye. A third electrode on the forehead served as an isolated ground. EMG activity was sampled at 500 Hz, and band-pass filtered between 30 and 500 Hz. Startle EMG response was rectified in a 200-ms window beginning 50 ms before the startle probe and smoothed using a 6-point running average. The startle amplitude was quantified as the peak response in a 150-ms post-probe window relative to the average activity in the 50 ms preprobe baseline period. Startle amplitude for each subject was converted to *T* scores to reduce between-subject variability unrelated to variables of interest. Comparable results, however, were obtained when raw scores were analyzed.

All measures were statistically evaluated through repeated measures ANOVA with the Greenhouse-Geisser correction applied. Generalization effects were examined using a 2 (BDNF genotype: Val/Val, Met carrying) × 4 (stimulus type: CS+, CS ± 20%, CS ± 40% and CS ± 60%) repeated measures ANOVA. To identify points on the stimulus continuum in which startle was reliably potentiated, paired sample *t* tests were performed relative to the CS ± 60% stimuli using Bonferroni’s correction for multiple comparisons (0.05/4 = 0.0125).

Results

BDNF genotypes

Of the 57 participants, 44 individuals carried the Val/Val *BDNF* allele (25 female), 10 carried the Val/Met allele (4 female) and 3 carried the Met/Met allele (1 female). Because of the relative infrequency of the Met/Met allele, and consistent with previous studies, individuals carrying at least one Met allele were grouped together and compared with individuals homozygous for the Val allele (Frodl *et al.* 2007; Hariri *et al.* 2003; Miyajima *et al.* 2008; Pezawas *et al.* 2004). The two groups did not differ in terms of gender [$\chi^2(1, N = 57) = 1.36, P > 0.20$] or ethnic composition [$\chi^2(5, N = 57) = 3.08, P > 0.60$].

Startle EMG

Figure 1 (top) presents startle *T* scores elicited during the ITI and presentation of all stimuli. Consistent with the impression from Fig. 1, startle magnitude varied as a function of stimulus type [$F(3,165) = 6.39, P < 0.001$]. However, this effect was qualified by a significant interaction with *BDNF* genotype [$F(3,165) = 3.90, P < 0.05$]; startle did not differ overall between *BDNF* genotypes [$F(1,55) < 1$]. [The Val/Val and Met-carrying groups (Val/Met and Met/Met) did not differ in terms of their ITI startle responses (mean = 40.01, SD = 9.33 and mean = 42.33, SD = 14.13, respectively, $t(55) = 0.70, P > 0.45$). Also, the Val/Val (mean = 128.64, SD = 54.08) and Met-carrying groups (mean = 131.92, SD = 45.16) did not differ in terms of selected shock intensity, $t(55) = 0.20, P > 0.80$. Moreover, we examined EMG activity elicited by the unconditioned stimulus itself: although Met-carrying individuals had numerically larger startle responses to the UCS (mean = 17.96, SD = 18.27) compared with the Val/Val individuals (mean = 10.92 mv, SD = 11.96), this difference did not reach significance $t(55) = 1.63, P > 0.10$. Finally, when EMG to the UCS was entered as a covariate in the repeated measures ANOVA, the significant interaction between stimulus type and *BDNF* genotype remained robust, $F(3,162) = 3.35, P < 0.05$].

Among those participants homozygous for the Val allele, *post hoc* comparisons confirmed that startle magnitude was potentiated (relative to the CS ± 60% stimuli) for both CS+ [$t(43) = 5.69, P < 0.001$] and CS ± 20% [$t(43) = 3.62, P < 0.001$] stimuli; there was a trend for startle potentiation to CS ± 40% stimuli [$t(43) = 1.91, P > 0.05$]. Overall then, individuals with the Val/Val genotype showed potentiation of their startle response to CS+ stimuli and generalized defensive responding to perceptually similar stimuli (i.e. CS ± 20%).

Importantly, Met-carrying individuals did *not* show the same relation between startle and stimulus type. Rather, Met allele carriers *only* showed a potentiated startle response to CS ± 20% stimuli [$t(12) = 3.30, P < 0.0125$]; Met allele carriers did not show a potentiated startle response to either CS ± 40% [$t(12) = 2.22, P < 0.05$] *or* CS+ [$t(12) = 0.54, P > 0.55$] stimuli.

Self-reported shock likelihood

Figure 1 (bottom) presents post-task ratings of shock likelihood for both Val/Val and Met allele carriers as a function of stimulus type. Although shock likelihood ratings varied as a function of stimulus type [$F(3,165) = 90.41, P < 0.001$], ratings did not differ as a function of *BDNF* genotype [$F(1,55) = 1.37, P > 0.20$] and *BDNF* genotype did not interact with

stimulus type [$F(3,165) < 1$]. Shock was rated as more likely following the CS+ stimuli relative to CS ± 60% [$t(58) = 13.23$, $P < 0.001$], CS ± 40% [$t(58) = 10.69$, $P < 0.001$] and CS ± 20% [$t(58) = 3.43$, $P < 0.001$] stimuli. Additionally, shock was rated as more likely following CS ± 20% compared with CS ± 40% [$t(58) = 15.20$, $P < 0.001$] and CS ± 60% [$t(58) = 21.03$, $P < 0.001$] stimuli; finally, shock was rated as more likely following CS ± 40% than CS ± 60% stimuli [$t(58) = 4.65$, $P < 0.001$]. Thus, shocks were perceived as being progressively likely as stimuli became more perceptually similar to the CS+.

Discussion

Participants in the current study *reported* that shock was more likely as stimuli resembled the CS+, despite the fact that *only* the CS+ was ever followed by an aversive shock. Indeed, individuals homozygous for the Val/Val *BDNF* polymorphism also showed an increase in startle response as stimuli were more perceptually similar to the CS+. That is, individuals with the Val/Val *BDNF* genotype showed a robust potentiation of the their startle response to both CS+ and CS ± 20% compared with CS ± 60% stimuli; indeed, there was a trend towards potentiation of the startle response to CS ± 40% stimuli as well. These results dovetail nicely with those reported by Lissek *et al.* (2008), who also found that perceived risk and startle potentiation were related to perceptual similarity of stimuli to a CS+.

However, a different pattern of startle potentiation was obtained among individuals carrying one or two Met alleles of the *BDNF* polymorphism. Specifically, Met allele carriers did not show potentiation of the startle response to CS+ stimuli. This group *did* show a potentiation of their startle response to CS ± 20% stimuli, suggesting that Met allele carriers were characterized by a *specific* deficit on CS+ trials. Thus, both Val/Val and Met-carrying groups showed comparable generalization of fear-potentiated startle to stimuli that were perceptually similar to the CS+; however, only the Val/Val allele carriers showed a robust potentiation of startle to the actual CS+. In fact, among Met allele carriers, startle response to the CS+ was most similar to the CS ± 60% stimuli – the most perceptually dissimilar stimuli to the CS+.

Importantly, *BDNF* groups did not differ in their post-task ratings of shock likelihood, chosen level of shock intensity or EMG response amplitude to the UCS itself. Thus, the observed deficits in startle potentiation to the CS+ do not simply reflect a lack of awareness of shock contingencies. Rather, the reduction in startle potentiation to the CS+ among Met allele carriers may reflect a specific abnormality in defensive responding – potentially reflecting abnormal amygdala-mediated learning. Indeed, work on transgenic mice suggests that the Met allele may specifically impair hippocampus-dependent context conditioning (Liu *et al.* 2004). The degree to which the generalization task employed here relies on functioning of the hippocampus is unknown. Future studies may wish to examine whether the observed pattern of results during a generalization paradigm would also be evident in a simpler CS+/CS− paradigm and in context-conditioning paradigms (cf. Liu *et al.* 2004).

These results add an important dimension to existing work on the Val66Met *BDNF* polymorphism. Although previous work has linked the Met allele to abnormal hippocampal structure and function (Dempster *et al.* 2005; Egan *et al.* 2003; Hariri *et al.* 2003; Pezawas *et*

al. 2004), the current study suggests that *BDNF* Met allele carriers are also characterized by deficient *fear* conditioning in this type of generalization paradigm. These results are generally consistent with recent nonhuman animal work on the fundamental role of BDNF during fear and context conditioning (Chhatwal *et al.* 2006; Conner *et al.* 1997; Jones *et al.* 2007; Liu *et al.* 2004; Ou & Gean 2006; Rattiner *et al.* 2004a,b; Yan *et al.* 1997) and suggest that BDNF might play a similar role in the acquisition of fear in humans.

These results have potential implications regarding mechanisms linking genetic variation in *BDNF* to risk for psychopathology. Among depressed patients for instance, recent studies have found that individuals who carry the Met allele of the *BDNF* gene have significantly reduced hippocampal volume (Frodl *et al.* 2007) and greater hypothalamic–pituitary–adrenocortical response to dexamethasone challenge (Schule *et al.* 2006). Reduced hippocampal volume and function have also been implicated in risk for posttraumatic stress disorder (PTSD; Gilbertson *et al.* 2002, 2006).

The current study raises the possibility that the Met allele of the *BDNF* polymorphism may place individuals at risk for forms of psychopathology such as depression and PTSD – and may do so by altering processes relevant to fear conditioning. Specifically, a deficient ability to elicit defensive responses to appropriate stimuli may underlie generalization of fear in PTSD following a trauma. In the case of incorrectly learned CS–UCS contingencies, aversive stimuli and events may be more unexpected, and the situations might be more stressful overall. These possibilities are consistent with the fact that the UCS and ITI startle magnitudes in the Met group were higher than Val/Val participants; future studies might further examine the UCS and ITI responses during cue and context conditioning as a function of *BDNF* polymorphism. In addition, it will be important to determine whether Met-related startle deficits relate to differences in memory and behavior – for instance, whether Met allele carriers are less likely to return for a second testing session and, among those who do, whether they would continue to show a reduced fear-potentiated startle response to the CS+ (cf. Ameli *et al.* 2001; Grillon & Davis 1997).

In summary, the present data suggest that individuals homozygous for the Val allele of the Val66Met *BDNF* polymorphism show a potentiation of the defensive startle response to CS + stimuli as well as perceptually similar stimuli that were never followed by an aversive shock (i.e. CS ± 20% stimuli). These results are consistent with a recent startle study on fear generalization by Lissek *et al.* (2008). Individuals carrying one or two Met alleles of the *BDNF* gene, however, were characterized by deficient fear-potentiated startle specifically to the CS+. This pattern of results was evident despite relatively normal generalization of potentiated startle to CS ± 20% stimuli and post-task ratings of shock likelihood comparable to the Val/Val group. These results are consistent with recent nonhuman animal work implicating BDNF in amygdala-based associative learning processes and suggest that the Met allele of the *BDNF* polymorphism relates to abnormal fear conditioning.

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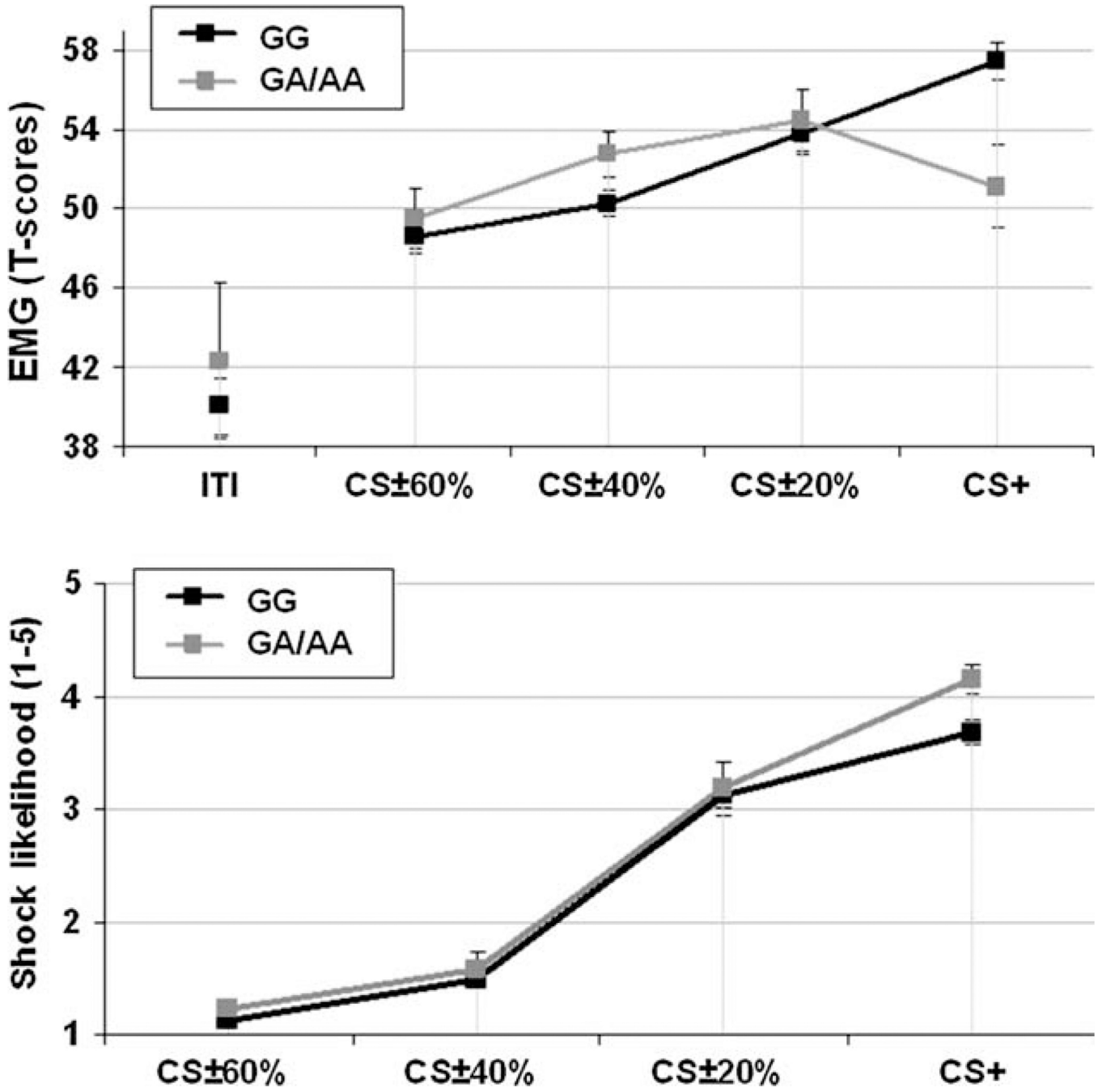

Figure 1. Startle response magnitude and post-task shock likelihood ratings as a function of stimulus type

Standardized EMG activity elicited by startle probes (top) and behavioural ratings of shock likelihood (bottom; 1 = “certainly not shocked”, 5 = “certainly shocked”) for each stimulus type for both individuals carrying the Val/Val *BDNF* genotype (*N* = 44) and those carrying one or two Met alleles of the *BDNF* genotype (*N* = 13).