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Brief Communications

# Reduced Serotonin Transporter Availability Decreases Prefrontal Control of the Amygdala

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After a threatening event, the risk of developing social psychopathologies is increased in short-allele (s) carriers of the serotonin transporter gene. The amygdala becomes overresponsive to emotional stimuli, an effect that could be driven by local hypersensitivity or by reduced prefrontal regulation. This study distinguishes between these two hypotheses by using dynamic causal modeling of fMRI data acquired in a preselected cohort of human s-carriers and homozygous long-allele carriers. Increased amygdala activity in s-carriers originates from reduced prefrontal inhibitory regulation when social emotional behavior needs to be controlled, suggesting a mechanism for increased vulnerability to psychopathologies.

## Introduction

The neurotransmitter serotonin plays an important role in regulating social and emotional processes (Canli and Lesch, 2007). Serotonergic signaling is affected by a serotonin transporter polymorphism (5-HTTLPR), of which short-allele (s) carriers (homozygous and heterozygous) show reduced serotonin transporter availability and serotonin reuptake compared with non-carriers (homozygous long-allele carriers) (Lesch et al., 1996). This genetic variation in s-carriers leads to a heightened amygdala response to social threat (Hariri et al., 2002; Heinz et al., 2005; Caspi et al., 2010) and increased risk for the development of social psychopathologies (Caspi et al., 2010). Stressful or traumatic events intensify this vulnerability (Caspi et al., 2003; Karg et al., 2011). The combination of genetic and environmental factors suggests two possible accounts of increased vulnerability (Pezawas et al., 2005; Canli and Lesch, 2007; Caspi et al., 2010; Hyde et al., 2011): s-carriers could have a heightened sensitivity to emotional stimuli or decreased top-down control over emotional processing. Distinguishing between these possible mechanisms is important to advance our understanding of human emotional processing and to target therapies toward either reducing emotional sensitivity or increasing emotional control (Hyde et al., 2011).

This study used dynamic causal modeling (DCM) (Friston et al., 2003) for fMRI, an analytical framework enabling tests of directionality in brain connectivity, to dissociate between those two mechanisms. Emotional processing was assessed with the social approach-avoidance (AA) task (Roelofs et al., 2009; Volman et al., 2011b), a well established protocol measuring behavioral and neural responses during automatic and controlled actions to emotional faces (Fig. 1A). Automatic response tendencies resulting in the approach of positive stimuli and the avoidance of negative stimuli are thought to be triggered by the amygdala (Quirk and Gehlert, 2003). When these emotional action tendencies need to be controlled during the AA task, the anterior prefrontal cortex (aPFC) has been shown to coordinate the contributions of several brain regions, including the amygdala (Volman et al., 2011a). Experimental alterations of the aPFC reduce emotional control and increase reactivity to emotional faces in the amygdala and in the fusiform face area (FFA) (Volman et al., 2011a). Here we assessed how physiological alterations of serotonin transporter availability influence the dynamics of this network during the production of automatic and controlled actions to emotional faces: via altered sensitivity or prefrontal control.

## Materials and Methods

### Participants

A total of 24 s-carriers (9 homozygous, 15 heterozygous) and 24 non-carriers were preselected with a double-blind design. All participants were right-handed male students with normal or corrected-to-normal vision and no history of neurological or psychiatric illness matched (between groups) for age (mean ± SD, 23 ± 2.6 and 22 ± 2.4 years), anxiety trait inventory (Spielberger, 1983; 32 ± 7.2 and 32 ± 5.4), depression (Beck et al., 1979; 2.8 ± 3.3 and 3.9 ± 3.2), and traumatic experiences (Nijenhuis et al., 2002; 1.75 ± 1.6 and 1.79 ± 1.6) (all $p > 0.2$, $F_{(1,46)} <$ 1.6). The first 20 participants were randomly selected and used in a related study (Volman et al., 2011b). The remaining participants were
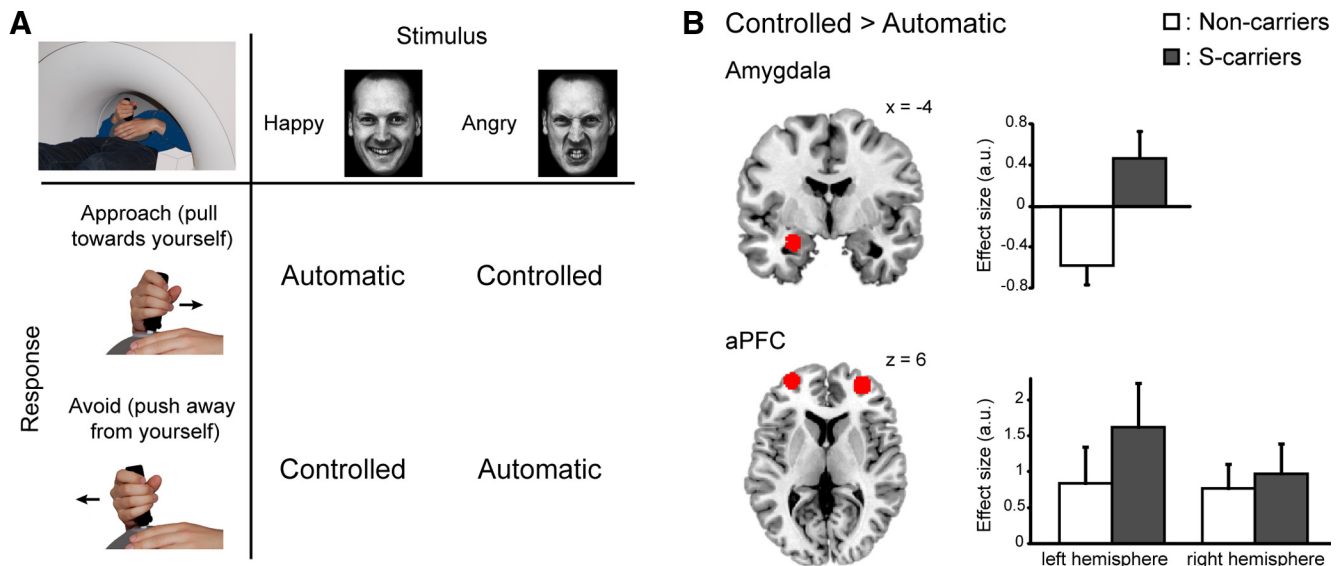
**Figure 1.** *A*, Design of the AA task. When viewing happy or angry faces, automatic stimulus-response tendencies trigger corresponding approach or avoidance actions. These tendencies could be followed during the automatic condition. In contrast, when task instructions required participants to avoid happy or approach angry faces, automatic tendencies needed to be controlled and overridden with the instructed response (controlled condition; Volman et al., 2011a). *B*, Regional effects of emotional control (controlled vs automatic trials) within amygdala (between-group differences) and aPFC (across groups). Left, SPM{*t*} overlapped on a representative brain (thresholded at *p* < 0.05 uncorrected for visualization). Right, Biased effect size of emotion control contrast ± SEM of the clusters presented on the left.

preselected based on their 5-HTTLPR genotype. All participants provided written informed consent according to the guidelines of the local ethics committee.

### Procedure and experimental tasks

The experimental setup, including tasks, salivary measurements, and imaging details, was as described previously (Volman et al., 2011b). Briefly, participants completed questionnaires and provided saliva, followed by the task-fMRI measurements, a resting-state scan (not reported here), and an anatomical scan. The AA task and an additional gender evaluation (GE) task were administered in two consecutive sessions (30 min each), with counterbalanced order across participants. Each task consisted of 24 blocks of 12 trials during which participants responded to visually presented faces by pulling a joystick toward themselves (approach) or by pushing it away from themselves (avoid). During the AA task, participants categorized faces as happy, angry, or neutral (filler items) based on their affective expressions. The combination of these emotion-response mappings introduced a distinction between more "automatic" conditions (approach-happy, avoid-angry) and "controlled" conditions (approach-angry, avoid-happy). We will refer to this factor as "emotional control": the additional processing required to overcome the prepotent response and to apply the counterintuitive rule. During the GE (control) task, participants categorized the gender (affectively irrelevant) of the same faces, thereby requiring no rule-driven action selection based on the emotion of the face (Roelofs et al., 2009). Each face was presented for 100 ms, preceded by a 300 ms blank screen and followed by the participant's response, a blank screen, and a pseudorandom intertrial-interval (1–3 s). A baseline period of 21–24 s preceded each block.

### Materials and apparatus

Functional MR images were acquired on a 1.5 T MRI scanner (Avanto; Siemens) with an 8-channel head coil using a multi-echo GRAPPA sequence (Poser et al., 2006) (TR 2.14 s, TEs 9.4/21/33/44/56 ms, 34 transversal slices, ascending acquisition, distance factor: 17%, effective voxel size 3.3 × 3.3 × 3.5 mm, FOV 212 mm). Anatomical MR images were acquired using a magnetization prepared rapid gradient echo sequence (TR 2250 ms, TE 2.95 ms, 176 sagittal slices, voxel size 1 × 1 × 1 mm, FOV 256 mm).
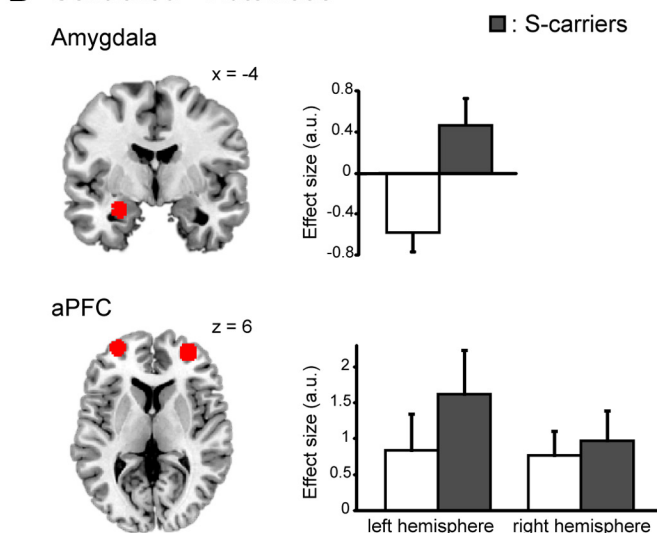
### DNA analysis

DNA was isolated from saliva using the Oragene system (DNA Genotek). Genotyping of the 5-HTTLPR polymorphism in the *SLC6A4* (*5-HTT, SERT*) gene was performed by simple sequence length analysis. PCR was on 50 ng of genomic DNA using 0.5 $\mu$M fluorescently labeled forward primer (FAM-5′-GGCGTTGCCGCTCTGAATGC-3′) and reverse primer (5′-GAGGGACTGAGCTGGACAACCAC-3′), 0.25 mM dNTPs, 1× PCR optimization buffer A [30 mM Tris-HCl, pH 8.5, 7.5 mM (NH$_4$)$_2$SO$_4$, 0.75 mM MgCl$_2$], 10% DMSO, and 0.4 U of AmpliTaq Gold DNA-polymerase (Applied Biosystems). The cycling conditions for the PCR were 12 min at 95°C, 35 cycles of 1 min at 94°C, 1 min at the optimized annealing temperature (57.5°C), 2 min at 72°C, followed by 10 min at 72°C. For quality control, 5% blanks and duplicates between plates were also taken. Determination of allele length was by automated capillary sequencing (ABI3730; Applied Biosystems).

### Behavioral analysis

Trials in which the joystick was moved in the wrong direction or those showing an extreme reaction time (RT; <100 or >1500 ms), joystick peak velocity or path length (>3 SD from subject-specific data distribution) were excluded (Volman et al., 2011b). If the error rate of a block was above chance level, the whole block was excluded. Median RTs were calculated and entered in a 4-way repeated-measures ANOVA (ANOVA-rm), with factors genotype (s-carriers, non-carriers), task (AA, GE), movement (approach, avoid), and valence (happy, angry). The *a*-level was set at *p* < 0.05.

### fMRI data: regional effects analyses

The imaging data were preprocessed as described previously (Volman et al., 2011b). Participant-specific fMRI time series were analyzed using a general linear model including the following effects for each task (AA, GE) separately: approach-happy, approach-neutral, approach-angry, avoid-happy, avoid-neutral, and avoid-angry. Trials excluded from behavioral analyses and instruction periods were modeled with separate regressors. The group-level random effects multiple regression analysis considered 16 conditions, given by the combination of four factors: genotype (s-carriers, non-carriers), task (AA, GE), valence (happy, angry), and condition (automatic, controlled), with testosterone and cortisol levels as condition-specific covariates (Volman et al., 2011b). The regions

of interest (ROIs) followed our hypotheses, namely amygdala from the aal atlas (Tzourio-Mazoyer et al., 2002) using the WFU PickAtlas tool (Maldjian et al., 2003) and aPFC from Volman et al. (2011a, 2011b) (two spheres; radius: 8 mm; centers: −30, 58, 2 and 32, 54, 8). Correction for multiple comparisons was implemented with small volume familywise error (FWE).

*fMRI data: DCM*
*Time series extraction.* fMRI time series representative of the left FFA, left amygdala, and left aPFC (Volman et al., 2011a) were selected on ROIs defined with anatomical and functional constraints (Stephan et al., 2010). The left aPFC anatomical search space was described above (regional effects analysis). The FFA space was a sphere (radius: 10 mm; center: −43, −54, −17) defined by a previous mapping study (Liu et al., 2010). The amygdala space was based on anatomical information obtained from individual MRI scans (FSL-FIRST v1.2; http://www.fmrib. ox.ac.uk/fsl/first; Patenaude et al., 2011). For each ROI in each participant, 20 voxels were selected that showed the strongest effect on an *F* test on main effect of happy and angry faces during the AA task from the first level model with an explicit baseline. The first eigenvariate across these voxels was extracted after removing variance explained by effects of no interest.

*DCM model specification.* Analysis of regional fMRI effects indicated increased aPFC responses across both genotypes and increased amygdala activity in s-carriers compared with non-carriers during emotional control (see Results). DCM was used to distinguish between the two hypothesized mechanisms accounting for the different amygdala response to emotional control in the two genotypes. We defined the basic model structure common across all models (Fig. 2A): presentation of a face as driving input in the FFA node (with RT as duration), forward projection from FFA to amygdala (Pessoa et al., 2002; Gschwind et al., 2012), and a bidirectional connection between amygdala and aPFC, after evidence of functional and anatomical connections (Bracht et al., 2009; Volman et al., 2011b).

Given this basic model, we tried to identify where emotional control modulated or enabled extrinsic or self-connections within this distributed system. Our model space addressed two key questions: (1) how emotional control modulated the aPFC response and (2) whether additional control-related changes in connection strengths were necessary to explain amygdala responses. This resulted in a factorial model space in which the first factor had four levels: emotional control changed the amygdala→aPFC connection, the aPFC self-connection, an additional FFA→aPFC connection, or it excited the prefrontal cortex directly. The second factor investigated whether the source of the amygdala modulation originated from the aPFC or from another unspecified region (Stephan et al., 2008). This factor had three levels with six variations in total: (1) a basic model (aPFC influences amygdala via aPFC→amygdala connection), (2) aPFC activity modulates FFA→amygdala connection and amygdala self-connection, or (3) emotional control modulates FFA→amygdala connection, amygdala self-connection, and acts as driving input on the amygdala. This model space allowed us to address the generation of differential responses in the aPFC by comparing families of models distinguished by the first factor (averaging over the second). These correspond to prefrontal families A–D in Figure 2C. Finally, we were able to address our key question about the prefrontal control of amygdala responses by comparing models with and without further emotion control effects. These are amygdala families A–C in Fig. 2C.

*Model inference.* For each factor, we tested which family of models best explained the data across all participants using the negative free energy approximation to log model evidence (Friston and Stephan, 2007). A random-effects Bayesian model selection procedure for model families (Penny et al., 2010) was used to derive the exceedance probability ($XP_k$; i.e., the probability that a particular model family k is more likely than any other model family considered, given the data). We also checked for differences in the optimal model or model ranking between genotype groups.

*Parameter inference.* We then compared the parameters of the winning families to test for genotype differences in emotional control of the amygdala. When it was not possible based on the model evidence to

distinguish between two families ($XP_k > 0.95$), Bayesian model averaging across all families with $XP_k > 0.05$ over genotypes was applied (Penny et al., 2010). Bayesian model averaging calculates an average parameter estimate for each connection and participant across a set of models, weighted by the posterior probability of each model. This procedure enables inference about model parameters while accounting for differences in model evidence. Next, a univariate GLM was created for each of the parameter estimates modeling emotional control to the amygdala. The reciprocal SD of that estimate was considered as a weight for least-squares regression to adjust for heteroscedasticity (Carroll and Ruppert, 1988). One outlier was present and removed (*post hoc* analyses with outlier produced similar results: genotype effect on aPFC→amygdala: $F_{(1,46)} = 12.5$, $p = 0.001$). The α-level was Bonferroni corrected (0.05/3 = 0.017).

## Results
### Behavioral data
Participants performed the tasks accurately (omissions: 0.9%; error rate: 6.8%; trials excluded due to block errors: 0.4%; anomalous kinematic responses: 5.8%) and consistently (Table 1). The 4-way ANOVA-rm showed a main effect of task ($F_{(1,46)} = 22.8$, $p < 0.001$), movement ($F_{(1,46)} = 4.2$, $p = 0.047$), valence ($F_{(2,45)} = 139.2$, $p < 0.001$), task × valence interaction ($F_{(2,45)} = 24.5$, $p < 0.001$), and an emotional control effect over both tasks (movement × valence; $F_{(1,46)} = 6.1$, $p = 0.017$). When considering each task separately, both tasks showed a valence effect (AA task: $F_{(1,46)} = 96.7$, $p < 0.001$, GE task: $F_{(1,46)} = 26.2$, $p < 0.001$). Only the AA task showed an emotional control effect ($F_{(1,46)} = 4.9$, $p = 0.032$; GE task: $p = 0.228$), as also found previously (Roelofs et al., 2009), indicating that controlled conditions evoked significantly longer RTs than automatic conditions. There was no evidence for genotype differences in RT or error rate (all $p > 0.05$).

### fMRI data: regional effects analyses
First, the amygdala showed a genotype (s-carriers > non-carriers) × condition (controlled > automatic) trend effect for the AA task (left side; $z = 3.09$, $p_{FWE} = 0.061$, coordinates of local maxima: −28, −4, −20, Fig. 1B). *Post hoc* testing indicated that this effect was mainly driven by angry faces ($z = 3.19$, $p_{FWE} = 0.046$, local maxima: −28, −4, −20) and less by happy faces ($z = 2.00$, $p_{uncorrected} < 0.05$, local maxima: −26, −6, −18). When masking the interaction with the three-way interaction (genotype [s-carriers > non-carriers] × task [AA > GE] × condition [controlled > automatic]), the effects did not change, indicating the results are specific for the AA task. Second, the left and right aPFC (BA 10) showed a stronger response for the controlled than for the automatic trials during the AA task ($z = 3.47$, $p_{FWE} = 0.021$, local maxima: −30, 60, 6, and $z = 3.50$, $p_{FWE} = 0.019$, local maxima: 32, 52, 6, respectively; Fig. 1B). When comparing the effects of the AA task with that of the GE task (by masking the contrast with the two-way interaction [task (AA > GE) × condition (controlled > automatic)]), the effects remained the same. This indicates that the results are specific to the (explicit) AA task, replicating previous reports on these tasks (Roelofs et al., 2009; Volman et al., 2011b).

### fMRI data: DCM
Formal model comparison indicated that, in the best models across genotypes, emotional control modulated the aPFC both via self-connection and amygdala feedforward input, whereas the amygdala was modulated via the aPFC (Fig. 2D,E).

Crucially, the strength of the direct aPFC→amygdala connection showed a significant genotype difference ($F_{(1,45)} = 6.8$, $p = 0.012$, Fig. 2E). This aPFC→amygdala connection had a negative
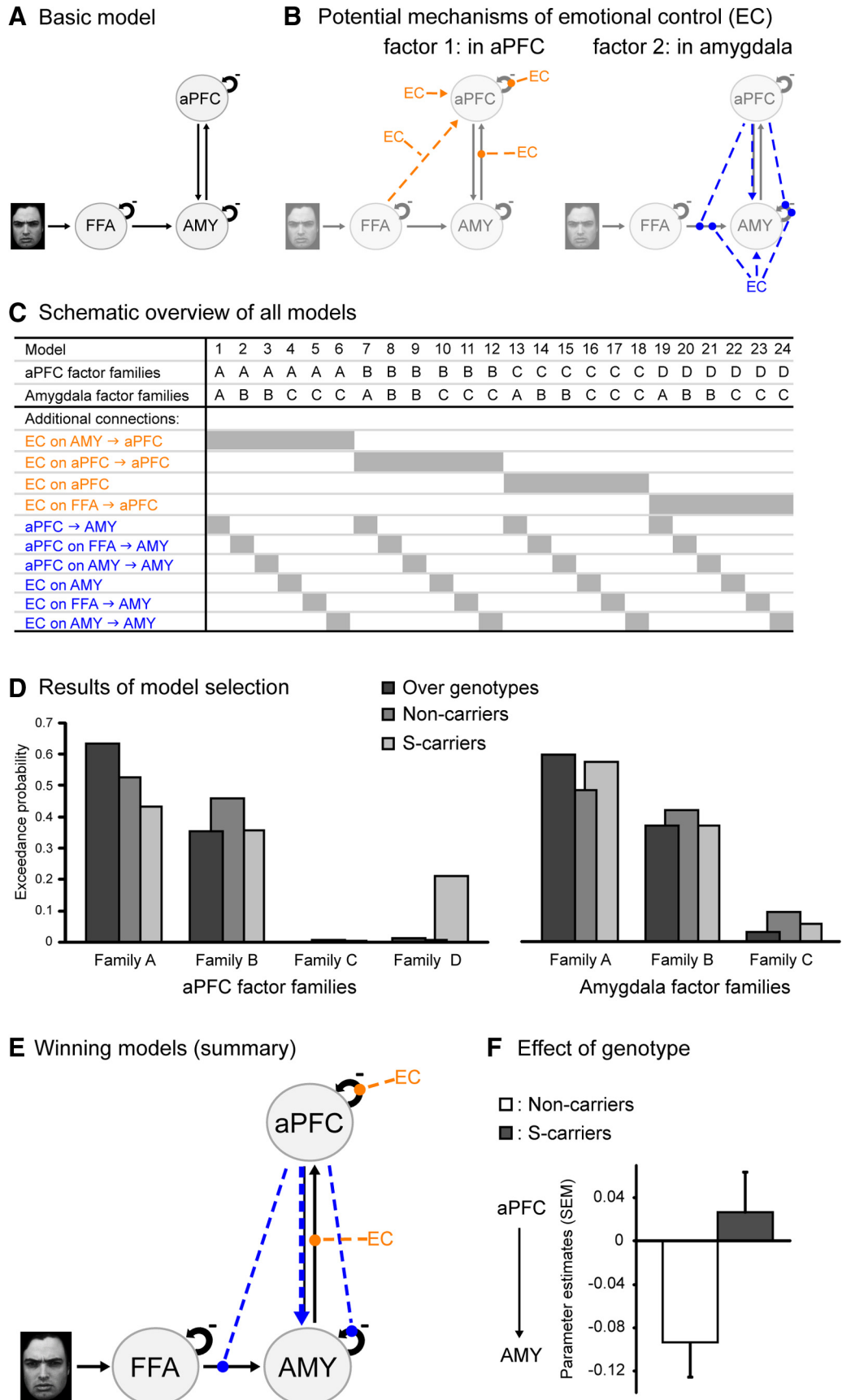
**Figure 2.** Modulation of interregional connectivity. **A**, Basic structure of the model: face presentation drives FFA activity, which projects to the amygdala (AMY) that is bidirectionally connected with aPFC. **B**, Emotional control could modulate aPFC (orange) and amygdala activity (blue) either directly, on connections, or via other nodes. **C**, Overview representing all 24 models and their corresponding families within each factor. Each model contained the basic model with one orange and one blue connection. **D**, XP$_k$ for each factor of the model selection (*Figure legend continues.*)

**Table 1. Mean RTs (SEM) in milliseconds**

| | S-carriers | | Non-carriers | |
|---|---|---|---|---|
| | Approach | Avoid | Approach | Avoid |
| AA-task | | | | |
| Happy | 524 (18) | 554 (20) | 517 (19) | 546 (21) |
| Neutral | 592 (19) | 598 (18) | 564 (20) | 583 (21) |
| Angry | 587 (19) | 583 (18) | 575 (20) | 587 (20) |
| GE-task | | | | |
| Happy | 509 (12) | 530 (17) | 511 (15) | 525 (15) |
| Neutral | 515 (13) | 528 (16) | 509 (16) | 524 (16) |
| Angry | 535 (14) | 543 (17) | 526 (16) | 539 (16) |

**Table 2. DCM parameters showing the estimated mean (SEM) in Hertz**

| Parameter | Over genotypes | Non-carriers | s-carriers |
|---|---|---|---|
| Faces to FFA | 0.08 (0.07) | 0.10 (0.11) | 0.07 (0.10) |
| FFA→AMY | 0.07 (0.03) | 0.08 (0.04) | 0.07 (0.05) |
| AMY→aPFC | −0.01 (0.05) | −0.05 (0.08) | 0.02 (0.07) |
| aPFC→AMY | −0.04 (0.03) | −0.09 (0.03) | 0.03 (0.04) |
| aPFC on FFA→AMY | −0.003 (0.002) | −0.003 (0.003) | −0.003 (0.002) |
| aPFC on AMY→AMY | −0.001 (0.001) | −0.002 (0.002) | −0.0004 (0.002) |
| C on AMY→aPFC | 0.02 (0.01) | 0.02 (0.02) | 0.02 (0.01) |
| C on aPFC→aPFC | 0.01 (0.01) | −0.004 (0.004) | 0.02 (0.01) |

weight for non-carriers ($F_{(1,23)} = 10.6$, $p = 0.003$), but was not significantly different from zero for s-carriers ($F_{(1,22)} = 0.5$, $p = 0.473$; Table 2). Indirect top-down aPFC modulations of the amygdala (amygdala factor family B) showed no group difference (both $F < 0.9$, $p > 0.3$).

In summary, the best explanation for control-related effects in the aPFC was an increase in amygdala→aPFC connectivity and aPFC self-connectivity. The subsequent prefrontal, control-related responses are then communicated back to the amygdala (with no need for emotional control modulations from other sources). However, the inhibitory aPFC→amygdala control effects are reduced in s-carriers, leading to disinhibited emotional amygdala responses.

## Discussion

Genetic differences associated with altered serotonin function influence functional and anatomical connectivity between the amygdala and ventral PFC (Heinz et al., 2005; Pezawas et al., 2005; Holmes, 2008; Pacheco et al., 2009). This study qualifies that alteration, showing that serotonin influences the ability of the aPFC to control amygdala reactivity to emotional faces. In s-carriers, automatic amygdala responses are not adequately inhibited by the aPFC when emotional control is required to facilitate an alternative course of action. The specificity of these connectivity effects was further qualified by analyses of regional activity and behavioral performance.

In this study, participants followed either their automatic response tendency to approach happy and avoid angry faces or they had to override that tendency with the opposite counterintuitive

←

(*Figure legend continued.*) for model families. For the aPFC factor, families 1 and 2 together show $XP_k > 0.95$. For the amygdala factor, $XP_k > 0.95$ is reached for families 1 and 2 together, all containing a modulation via the aPFC. These $XP_k$ values are similar for non-carriers (medium gray), s-carriers (light gray), and across groups (dark gray). *E*, Best models (combined $XP_k > 0.95$) for the fMRI data across genotypes in which emotional control modulated the aPFC and aPFC modulated the amygdala. These models were averaged within subjects for parameter inference. *F*, Parameter estimates ($\pm$ SEM) of the direct aPFC→amygdala connection. Non-carriers, but not s-carriers, showed significant inhibition of amygdala by the aPFC.

stimulus-response mapping (happy-avoid, angry-approach). The amygdala is thought to trigger automatic emotional response tendencies, whereas during emotional control, the aPFC is suggested to coordinate the involvement of several brain regions, including the amygdala (Quirk and Gehlert, 2003; Volman et al., 2011a). Exerting emotional control evoked stronger amygdala activity in s-carriers, whereas aPFC activity and behavioral performance was comparable across groups. These findings indicate that reduced aPFC inhibition in s-carriers was not a by-product of between-group differences in aPFC activity or behavior. They also provide evidence that reduced inhibitory coupling from aPFC to amygdala in s-carriers can explain enhanced amygdala activity when emotional control is required. Finally, these effects were specific for emotional control: they were significantly stronger in the AA task compared with an additional task with the same stimuli and emotionally irrelevant instructions (Roelofs et al., 2009).

A strong emotional event such as stress or trauma results in a strong amygdala response, increasing the bias for automatic emotional behavior (Quirk and Gehlert, 2003). In s-carriers, a lack of prefrontal control reduces the possibility of inhibiting these biases. The enhanced expression of automatic tendencies explained by this connectivity-based mechanism could account for the increased stress sensitivity and vulnerability to social psychopathologies observed in s-carriers, but also their heightened sensitivity for all motivationally relevant inputs (Lesch et al., 1996; Canli and Lesch, 2007; Caspi et al., 2010; Homberg and Lesch, 2011).

The present results suggest that anterior prefrontal inhibition of the amygdala is an important mechanism during control of social emotional actions, and a reduction thereof is a risk factor for the development of social psychopathologies. Several studies focused on assessing the neural mechanisms of a diverse range of psychopathologies support this theory, showing that prefrontal-amygdala coupling was affected during emotional processing (Kim et al., 2011; Rudie et al., 2012; Strakowski et al., 2012). A recent DCM study even demonstrated reduced effective connectivity from the PFC to the amygdala in patients with depression (Almeida et al., 2011) often associated with serotonin dysfunction (Holmes, 2008). Furthermore, humans and animals studies that focus on lesions of the aPFC and the adjacent orbital frontal cortex reported reduced control of social and emotional behavior (Damasio et al., 1994; Berlin et al., 2004; Agustín-Pavón et al., 2012). Reduced functionality of the aPFC induced by transcranial magnetic stimulation also decreased the ability to apply emotional control while at the same time enhancing activity of the amygdala (Volman et al., 2011a).

To conclude, this effective connectivity study shows that a lack of prefrontal inhibitory regulation underlies the increased amygdala response in individuals with reduced serotonin reuptake (s-carriers) during control of social emotional behavior. This result suggests that increasing emotional control would be an effective therapeutic intervention for preventing the emergence of social psychopathologies in s-carriers. For example, explicitly instructed emotion regulation strategies can reduce 5-HTTLPR-related amygdala differences (Schardt et al., 2010). Moreover, improving the capacity to exert emotional control might be a (preventive) strategy for s-carriers in case they need to be prepared for challenging situations, for example, in stressful professions.

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