Self-regulation of impulsivity via maturation of the executive resources benefits our well-being. The review of behavioral, neuroimaging, and pharmacological studies appears to provide evidence of a relationship between the self-regulation of impulsivity, activity of the prefrontal cortex, and serotonergic neurotransmission. Although a wide range of genetic, developmental, and social factors exists, much of this information, their interactive mechanisms in particular, remains to be clarified. Thus, in the present article, I first review the brain functions that underlie self-regulative processes and then provide an update on recent findings regarding serotonergic neurotransmission. Next, by integrating findings from behavioral genetics that examine the association between gene polymorphism and impulsivity, I discuss the bright sides of the risk allele of gene polymorphism. Finally, I argue the future direction of genetic and environmental bidirectional studies.

Key words: self-regulation, VLPFC, serotonin, gene polymorphism, gene environment interaction

Self-regulation of actions, thoughts, and emotions accomplished by maturation of the executive resources are the constituents of happiness. As childhood self-control predicts physical health, substance dependence, personal finances, and criminal behavior outcomes (Moffitt et al., 2011), self-regulation seems to be essential and beneficial to our well-being. Self-regulation comprises a wide spectrum of human behaviors and requires several processes including flexibility, attentional set shifting, and response inhibition to override impulses (Baumeister, 2002). Response inhibition, the main focus of the present review, is one aspect of impulsivity control (Monterosso & Ainslie, 1999). Impulsivity may be associated with a wide range of clinically relevant behaviors, including pathological gambling and eating disorders (Barratt, 1994; McMurran, Blair, & Egan, 2002). Behavioral impulsivity has been thought to involve two broad aspects: reward-delay impulsivity, defined as an inability to delay the acquisition of rewards, leading to an increased tendency to select immediate small rewards over larger delayed rewards; and rapid-response impulsivity, the failure to successfully inhibit a behavioral response to one’s environment or social context.

Here, I review the brain functions that underlie self-regulative processes and provide an update regarding recent findings pertaining to serotonergic neurotransmission that are

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thought to be related to self-regulation in general. In addition, I discuss research that associates gene polymorphism and impulsivity, argue the bright side of the risk allele of the serotonergic gene polymorphism, and propose a future direction for genetic and environmental bidirectional studies.

**ENVIRONMENTAL INFLUENCES ON SELF-REGULATION AND PREFRONTAL CORTEX FUNCTION**

The ability to inhibit planned or ongoing actions is an important control mechanism that facilitates efficient reactions in response to sudden environmental changes (de Jong, Coles, Gratton, & Logan, 1990). Brain neuroimaging studies, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have shown that higher cognitive-controlled functions draw heavily on the prefrontal cortex, including the ventrolateral prefrontal cortex (VLPFC), the right side of which is well known to be critical to the inhibitory process in general (Garavan, Ross, & Stein, 1999; Horn, Dolan, Elliott, Deakin, & Woodruff, 2003; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998). Lesion studies of the human brain have shown that patients with right frontal damage involving VLPFC exhibit less efficient behavioral inhibition than those with corresponding left frontal damage (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Aron, Monsell, Sahakian, & Robbins, 2004). Furthermore, clinical findings of patients with schizophrenia or mania who exhibit impulsivity as a major personality trait show decreased activation of the right VLPFC during Go/No-Go tasks (Mazzola-Pomietto, Kaladjian, Azorin, Anton, & Jeanningros, 2009; Kaladjian et al., 2007).

Inhibitory function of the VLPFC is also known to regulate affective responses by modulating the activity of the amygdala through the cortical–subcortical pathways (Lieberman et al., 2007; Nomura et al., 2004; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008a, 2008b). Upon development of the emotional contagion system, which is mainly based on subcortical areas, one person can be automatically affected by another person’s affective state without even being aware of it (Hatfield, Rapson, & Le, 2009). On the other hand, depending on executive resources, the use of cognitive perspective taking (PT) enables us to intentionally and consciously understand the thoughts and feelings of others by imagining their perspectives. Nomura, Ogawa, and Nomura (2010) found that activity in the right VLPFC while an individual imagined the perspective of others varied by social relationship (Fig. 1). As a pre-treatment, participants played a game with opponents who were playing either fairly or unfairly. The prefrontal activities were measured using near-infrared spectroscopy (NIRS) while each participant evaluated their partner’s face. The data showed that taking the perspective of a person acting unfairly by observing the happy expression on their face activated the right VLPFC in participants with high-PT ability, suggesting that when a high-PT person took another’s perspective and evaluated their emotions, any bottom-up negative emotions arising from a processing of the emotional contagion would be inhibited. That is, the high-PT person would effectively inhibit their negative emotions when taking the perspective of an unfair player.
Fig. 1. Results of Nomura et al., (2010). The mean concentration changes in oxygenated hemoglobin (oxy-Hb) during the hemodynamic response in the right ventrolateral prefrontal cortex (VLPFC).
(a) In the unfair condition, oxy-Hb concentrations significantly increased in the right side of the ventrolateral prefrontal cortex while taking the other's perspective as compared to self-perspective. As a pretreatment, the relationship between the participants and others (fair players, unfair players, and neutral players) were manipulated through a sequential prisoner’s dilemma game. The fair player sets the cooperation rate to 80%, the unfair player, on the other hand, sets the cooperation rate to 20%. Next, the participants were measured brain activity during viewing the facial expression of the opponents and adopt either of the two perspectives (self-perspective vs. other perspective). It must be noticed that this effect was limited to the high-perspective taking group. The participants were divided into 2 groups based on the perspective-taking scale of a Japanese version of the Interpersonal Reactivity Index (Davis, 1983): 19 participants with a high perspective-taking ability (High-PT: mean ± SD, 24.79 ± 1.76) and 18 participants with a low perspective-taking ability (Low-PT: mean ± SD, 18.83 ± 1.89).
(b) Results of Nomura et al., (2010). Oxy-Hb concentrations significantly increased on the right side of the VLPFC while participants considered the perspective of another person compared to their own self-perspective. This effect was limited to the High-PT group. The averaged oxy-Hb concentration time changes in the right VLPFC hemodynamic response. The gray zone indicates the task interval times while the white zone indicates the rest interval times in the unfair and the other person’s perspective condition. PT, perspective taking.
In summary, the right VLPFC plays a key role in the processing and regulation of affective and motor impulsive responses and leads our behavior adaptation to our environment. Both inhibition and the ability to orient toward goals and flexibly control actions according to the contingencies between one’s responses and the rewarding or punishing outcomes in the environment also seem essential. It is important that we determine whether the VLPFC modulates behavior according to the reward structure of the context. For instance, the right VLPFC is correlated with the probability of improving motor reaction times during the next trial in response to the omission of a cued monetary reward (Wrase et al., 2007). Masui, Kashino, and Nomura (2009) also found that variations in reward/punishment feedback effectively modulate right VLPFC activation within the neural network that is engaged by the Go/No-Go response-inhibition task. They showed that, although the reward for correct responses increased activity in the right VLPFC compared to punishment feedback, the reward/punishment feedback did not affect behavioral measures (errors or reaction times). These previous findings suggested that the behavioral adaptations accomplished by different neural processing are similar according to environment structure of the rewarding or punishing outcomes.

**HOW DOES SEROTONERGIC NEUROTRANSMISSION AFFECT IMPULSIVITY?**

Attraction to external stimuli that have rewarding properties is a central concept that underlies many normal and abnormal behaviors (Cools et al., 2005a; Robbins & Everitt, 2003). As an internal factor, serotonin (5-HT) has a wide range of biological effects on human, nonhuman primate, and rodent behaviors, and 5-HT neurotransmission dysfunction in the central nervous system may cause behavioral diseases characterized by impulsivity. Serotonergic antidepressant, antipsychotic, and anxiolytic drugs have been used in the treatment of neuropsychiatric disorders characterized by impulsivity, such that the administration of the serotonin-releasing drugs d,l-fenfluramine and paroxetine decreases impulsivity in patients with conduct disorders (Cherek & Lane, 2000).

VLPFC dysfunction, which causes impulsive behavior, results in brain functions being modulated by serotonin (Leyton et al., 2001). Kaye et al., (2001) also revealed this correlation by showing reduced binding of 5-HT	extsubscript{2A} – one of the 5-HT receptor subtypes – in the VLPFC in women who had recovered from bulimia nervosa, which is characterized by impulsive behavior, using PET imaging with [18F]altanserin to characterize 5-HT	extsubscript{2A} receptor binding. These pharmacological and neuroimaging studies appear to support the hypothesis that functional alteration in 5-HT neurotransmission due to genetic polymorphisms of the 5-HT receptors is involved in the expression and regulative processing of impulsive behavior in humans.

On the other hand, there are considerable numbers of replication failures with regard to correlation between serotonergic neurotransmission and impulsivity as have previously been described in acute tryptophan depletion (ATD) studies. ATD causes decreased 5-HT neurotransmission and is widely used to study the roles of serotonergic transmission in behavior, mood, and neural activity (Cools et al., 2005b; Fusar-Poli et al., 2006;
Mendelsohn, Riedel, & Sambeth, 2009). Plasma levels of tryptophan, a precursor of serotonin, were observed to be decreased after the drinking of an amino acid mixture lacking tryptophan, which allowed us to directly control the functional alteration of serotonergic neurotransmission due to ATD being a chemical factor of an individual's environment. This, in turn, enabled us to see the causality of the serotonin effect on brain function, cognition, and behavior. Early ATD studies showed that ATD increases rapid-response impulsivity in participants with a positive history of Alcoholism (LeMarquand et al., 1999) and in healthy adults during a continuous performance test (Walderhaug et al., 2002). However, in a recent study, no effect of ATD on rapid-response impulsivity during a stop-signal task was reported in healthy adults (Clark et al., 2005; Cools et al., 2005a); as such, this issue seems to be controversial in terms of motor functioning.

**SEROTONERGIC GENE AFFECTS IMPULSIVITY ACCORDING TO ENVIRONMENT STRUCTURE OF THE REWARDING OR PUNISHING OUTCOMES**

How do serotonergic gene polymorphisms play distinctive roles in regulating the process of impulsivity according to environment structure? In this section, we focus on the effect of the 5-HT\textsubscript{2A} receptor gene and the 5-HT transporter-linked gene polymorphism (5-HTTLPR) on impulsivity.

**5-HT\textsubscript{2A} GENE POLYMORPHISM**

The promoter region of the 5-HT2A gene includes a single nucleotide polymorphism, A-1438G, that has been reported to be associated with psychiatric disorders characterized by impulsive behavior, such as obsessive compulsive disorder and alcohol dependence (Preuss, Koller, Bondy, Bahlmann, & Soyka, 2001). Elevated frequencies of the A allele were also reported to be associated with susceptibility to anorexia nervosa (Collier et al., 1997) and criminal behavior by Swedish males (Berggard et al., 2003). Although no associations between 5-HT2A receptor gene polymorphisms and anorexia nervosa (Ziegler et al., 1999) or bipolar affective disorder (Robertson, Jones, Middle, Moray, & Craddock, 2003) have been reported, behavioral studies in healthy adult humans support the idea of a significant association between them in the continuous performance task and the Go/No-Go task. Nomura et al. (2006) discovered that a gene polymorphism in the 5-HT2A receptor (A-1438G) modulates impulsive behavior (responses for non-target stimuli) in a Go/No-Go task and indicated that incentive feedback in the results of the participants’ responses signifies individual differences. However, no difference was observed in reaction times (Table 1). This finding is consistent with the results of studies that demonstrated increased commission errors in psychopaths (Newman & Kosson, 1986) and aggressive male adolescents compared to nonaggressive male adolescents (LeMarquand, Benkelfat, Pihl, Palmour, & Young, 1999). Interestingly, they observed no difference in omission errors, a measure that is not supposed to be related to impulsivity,
even after controlling for group differences with regard to age, years of education, or gender. The current results further suggest that the A-1438G 5-HT2A receptor gene polymorphism is not significantly associated with the 7 personality dimensions except self-directedness evaluated by the Temperament and Character Inventory (TCI).

These results are consistent with those of other reports (e.g., Kusumi et al., 2002) showing that the 5-HT receptor function measured by 5-HT–induced intraplatelet Ca\textsuperscript{2+} mobilization has no significant association with the TCI, including the harm avoidance scale in which the serotonergic system is supposedly involved. Thus, inconsistency among those association findings may be accounted for by the use of categorical diagnostic criteria alone and statistical powers that do not provide adequate measures for identifying psychiatric phenotypes and subtle individual differences between the mental

### Table 1. Characteristics of Male and Female Subjects and TCI Scales in Subjects Sorted by 5-HT Receptor A-1438G Genotypes. HIT, Responding to Go Stimuli. CER, Responding to NoGo Stimuli.

<table>
<thead>
<tr>
<th></th>
<th>G/G</th>
<th>A/G</th>
<th>A/A</th>
<th>ANOVA</th>
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<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>40</td>
<td>16</td>
<td></td>
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<tr>
<td>Men</td>
<td>0.60</td>
<td>0.51</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>30.2 ± 13.4</td>
<td>27.8 ± 8.2</td>
<td>30.9 ± 11.4</td>
<td>0.65, 0.52</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.6 ± 4.0</td>
<td>15.3 ± 3.9</td>
<td>15.6 ± 45</td>
<td>0.25, 0.77</td>
</tr>
<tr>
<td>Reaction time (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIT RP</td>
<td>579.2 ± 67.7</td>
<td>571.5 ± 78.2</td>
<td>577.0 ± 81.3</td>
<td>0.07, 0.92</td>
</tr>
<tr>
<td>PP</td>
<td>574.6 ± 68.3</td>
<td>582.6 ± 88.3</td>
<td>583.3 ± 75.0</td>
<td>0.01, 0.99</td>
</tr>
<tr>
<td>RR</td>
<td>580.7 ± 7.6</td>
<td>576.1 ± 9.5</td>
<td>573.1 ± 9.8</td>
<td>0.01, 0.98</td>
</tr>
<tr>
<td>PR</td>
<td>582.0 ± 11.2</td>
<td>583.0 ± 9.4</td>
<td>571.6 ± 10.4</td>
<td>0.01, 0.99</td>
</tr>
<tr>
<td>CER RP</td>
<td>537.5 ± 86.1</td>
<td>549.6 ± 73.2</td>
<td>549.2 ± 78.6</td>
<td>0.04, 0.96</td>
</tr>
<tr>
<td>PP</td>
<td>549.2 ± 75.2</td>
<td>541.6 ± 68.3</td>
<td>543.3 ± 86.6</td>
<td>0.08, 0.91</td>
</tr>
<tr>
<td>RR</td>
<td>537.1 ± 89.7</td>
<td>552 ± 78.2</td>
<td>535.6 ± 71.6</td>
<td>0.04, 0.96</td>
</tr>
<tr>
<td>PR</td>
<td>550.9 ± 78.8</td>
<td>551.1 ± 65.5</td>
<td>535.9 ± 98.8</td>
<td>0.10, 0.91</td>
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<tr>
<td>Temperament scales</td>
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<tr>
<td>Novelty seeking</td>
<td>50.9 ± 6.5</td>
<td>50.5 ± 5.1</td>
<td>53.6 ± 9.3</td>
<td>1.05, 0.36</td>
</tr>
<tr>
<td>Harm avoidance</td>
<td>55.1 ± 6.6</td>
<td>51.5 ± 9.2</td>
<td>56.2 ± 11.9</td>
<td>1.43, 0.24</td>
</tr>
<tr>
<td>Reward dependence</td>
<td>42.4 ± 3.8</td>
<td>42.8 ± 5.1</td>
<td>40.8 ± 5.7</td>
<td>1.28, 0.31</td>
</tr>
<tr>
<td>Persistence</td>
<td>13.6 ± 1.7</td>
<td>14.0 ± 3.0</td>
<td>13.3 ± 2.5</td>
<td>0.34, 0.71</td>
</tr>
<tr>
<td>Character scales</td>
<td></td>
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</tr>
<tr>
<td>Self-directedness</td>
<td>66.4 ± 9.2</td>
<td>71.7 ± 10.1</td>
<td>69.6 ± 9.2</td>
<td>7.21, 0.01*</td>
</tr>
<tr>
<td>Cooperativeness</td>
<td>70.0 ± 6.4</td>
<td>71.1 ± 7.3</td>
<td>69.3 ± 8.1</td>
<td>0.32, 0.73</td>
</tr>
<tr>
<td>Self-transcendence</td>
<td>28.7 ± 5.8</td>
<td>27.4 ± 4.9</td>
<td>27.9 ± 6.3</td>
<td>0.27, 0.76</td>
</tr>
</tbody>
</table>

\*p < 0.05
characteristics of healthy and clinical subjects. Thus, the etiology of these complex
diseases, including their subtle differences, should be considered and elucidated using a
direct behavioral study that examines the relationship between genetic factors and
impulsive disease susceptibility in addition to the psychometric self-report approach to
impulsivity, which could ultimately provide a plausible explanation (Nomura & Nomura,
2006).

5-HTTLPR GENE POLYMORPHISM:
RISK ALLELE TURNS OUT TO BE BRIGHT

A variety of studies has shown that the short (S) allele of the 5-HTTLPR gene
SLC6A4 leads to excess 5-HT in the synaptic cleft as a result of the production of lower
concentrations of 5HTT mRNA and less 5-HT reuptake compared to the L-allele group
(Lesch, et al., 1996). The motor regulatory process, the main topic of this article, does not
seem to be influenced by 5-HTTLPR, as shown in several studies using the continuous
performance test and the stop-signal task (Clark et al., 2005), both of which require
withholding of an ongoing or dominant motor response.

The biochemical mechanism of the 5-HTTLPR gene is thought to result in enhanced
neural processing of the amygdala, particularly during presentation of negative adverse
environmental cues. Thus, the S-allele of the 5-HTTLPR gene could relatively increase
neuroticism, anxiety (Kaufman et al., 2004), and emotional regulation disorders in the
context of early and adult life adversity (Caspi et al., 2003). Therefore, mainstream
research focused on the negative effects of 5-HTTLPR polymorphism (see reviews Canli
& Lesch, 2007; Caspi, Hariri, Holmes, Uher, & Moffitt, 2010). These observations led to
the idea that 5-HTTLPR function does not directly affect the behavioral regulatory process
itself, the single specific dimension of cognitive function, but possibly via evaluation of
the potential risk accompanied by particular behavioral outputs.

Nomura et al., (2011) tested this hypothesis and found that the 5-HTTLPR genotype
effect on the motor regulatory process was seen in the punishment feedback condition
during a Go/No-Go task in a Japanese population. They identified that while monetary
punishment was given for impulsive behavior (responses for non-target stimuli), the S/S
homozygous made fewer commission errors than the L-allele carriers. Given that the S/S
homozygous of the 5-HTTLPR gene could relatively increase neuroticism or anxiety, this
result is consistent with our earlier study showing the positive correlation between a high
tendency toward neuroticism and a more inhibited response style in a Go/No-Go task
when it entailed the probability of receiving punishment (Masui et al., 2009). Such
cautious participants who are also willing to take risks became more cautious after their
lack of inhibition was punished, which was reflected in the latency of the consequent
reaction time trials in the stop-signal task (Rodriguez-Fornells, Lorenzo-Seva, & Andrés-
Pueyo, 2002). These findings led to the notion that changes in the motor inhibition
adoption strategy could be affected by various factors including biological traits in
addition to the 5-HTTLPR gene.
Recently, several studies have shown that the 5-HTTLPR S-allele is associated with improved cognitive function (See review, Homberg & Lesch, 2010). Homberg and Lesch (2010) insist on the bright side of the 5-HTTLPR S-allele by explaining that the environment shapes the outcome of these fundamentally neutral common genetic factors, leading to negative outcomes, but also has the potential for positive behavioral manifestation. As these factors may counteract or completely offset the negative consequences of anxiety-related traits, it can be hypothesized that both direct improvement of cognitive function and vulnerability such as oversensitivity to punishment could contribute to behavioral self-regulation under certain environmental conditions. In sum, risk alleles of gene polymorphisms such as the S-allele of the 5-HTTLPR sometimes exert both maladaptive and beneficial effects. Therefore, we should carefully see both the bright and the dark side of gene polymorphisms.

**CONCLUSIONS AND FUTURE DIRECTIONS: FROM CENTRAL DOGMA TO EPIGENESIS**

Research to date has focused largely on behavioral, psychophysiological, and genetic properties of the individual differences of the self-regulative process. However, the questions of whether and how a wide range of factors such as developmental, genetic, socio-environmental, and all of these interactive mechanisms are involved in the self-regulative process remain poorly understood. As Moffitt et al. (2010) showed that childhood self-control predicts physical health, substance dependence, personal finances, and criminal outcomes by following a cohort of 1000 children from birth to the age of 32 years, we should determine when and how genes require environmental and behavioral input to function appropriately during the normal course of human development.

Some recent studies offer several important suggestions on how to tackle this important question. For instance, Mills-Koonce et al. (2007) examined bidirectional genetic and environmental influences on mother and child behavior based on the family systems theory in which individual dyads operate within a hierarchy of the parent–child subsystem (Cox & Paley, 2003). By focusing on candidate genes for the reward sensitivity called dopamine receptor D2 (DRD2) gene polymorphism, they revealed that DRD2 Aþ1, which is considered to be related to affective vulnerability, in mothers and children relate to poor maternal sensitivity which was evaluated by qualitative ratings for parent-child interaction during free-play session. In addition, they found that child DRD2 polymorphism was not associated with later affective problems, the negative bivariate association with maternal sensitivity was maintained. Importantly, they also showed that maternal sensitivity itself moderates the association between DRD2 Aþ1 and affective problems at age 3 for children. These finding partially imply that epigenetic remodeling might occur in response to the socio-environmental activation of synaptic plasticity that regulates neural development and function (Bagot & Meaney, 2010).

In summary, we could gain a detailed insight into those mechanisms that is supposed to be related to constituents of happiness by examining psychological studies measuring
biochemical and pharmacological serotonergic functions, especially those investigating the effect of gene polymorphism that appear to provide a useful approach to clarifying the complex bidirectional genetic and environmental influences on self-regulation.

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