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SSRI-Induced Emotional Blunting: A Study of Cognitive Changes in Pharmaceutically Treated Depression

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SSRI-INDUCED EMOTIONAL BLUNTING: A STUDY OF COGNITIVE CHANGES IN PHARMACEUTICALLY TREATED DEPRESSION

by

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This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy

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ABSTRACT

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Objective: In recent years, approximately 12.7% of the American population are on a prescribed antidepressant medication. Selective Serotonin Reuptake Inhibitors (SSRIs) are a widely used pharmacological treatment for depressive and anxiety disorders, primarily due to their tolerance levels, mild side effects in comparison to other antidepressants, and broad range of clinical indications. However, there are still numerous concerns about SSRIs' ability to improve depressive symptoms without adding side effects such as sexual dysfunction, gastrointestinal upset, and a restricted range of emotions. Although patients typically claim that they have less emotional pain while on SSRIs than they do during a depressive episode, they also report feeling constrained in the range of emotions they experience, such as the inability to cry or feel enjoyment. When linked to antidepressant treatment, this phenomenon has been described as *emotional blunting*, or a numbing of emotion. While emotional blunting has been established qualitatively, detecting emotional blunting can be difficult for both patients and clinicians since patients may have little insight about the side effect. This study specifically seeks to address gaps in the literature by collecting information on subjects with long-term SSRI use for depression. This work explores the breadth of emotional blunting in long-term SSRI-users by determining if emotional blunting can alter cognitive processing of emotional information.

Participants and Methods: One hundred and twenty-two adults (61 controls and 61 SSRI-users with remitted depression) participated in an online survey. SSRI-users reported on emotional

blunting, mood, demographic characteristics, and SSRI-related side effects including sexual dysfunction. All participants were asked to identify emotional expressions via a facial Affect Naming task and attend to emotionally charged words with accuracy and speed via an Emotional Stroop task.

Results: Findings revealed that SSRI-users who reported sexual dysfunction were more likely than SSRI-users without sexual side effects to experience SSRI-induced emotional blunting. Contrary to hypotheses, there were no differences in identifying or processing emotional stimuli between controls and SSRI-users, between SSRI-users with and without subjective emotional blunting, or between SSRI-users with or without sexual dysfunction.

Discussion: The connection between sexual dysfunction and emotional blunting in long-term SSRI-users has been established and needs further exploration, as the two side effects may follow similar biological pathways and have relevant clinical implications on pharmacologically treating depression. Further study of the overlap between sexual dysfunction and emotional blunting will allow prescribers to find optimal dosages while taking into consideration the significant social side effects demonstrated in many long-term SSRI-users. Other clinical implications include the need to elucidate objective and accessible ways to measure SSRI-induced emotional blunting in long-term SSRI-users. While emotional blunting in SSRI-users was not detectable through cognitive assessments in the current study, physiological changes in SSRI-users may provide an objective way to measure emotional blunting, as these reactions are less likely to be impacted by conscious awareness and may be more sensitive to subtle nuances. Ultimately, it is crucial that antidepressant prescribers become more aware of emotional blunting, recognize its overlap with sexual dysfunction, and find a way to objectively track it over time in order to provide optimal care to patients with depression.

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1. Introduction

In recent years, approximately 13% of American adults are on a prescribed antidepressant medication (Kantor et al., 2015). Selective Serotonin Reuptake Inhibitors (SSRIs) are the first-line pharmacological treatment for depressive disorders, primarily due to their tolerance levels, mild side effects in comparison to other antidepressants, and broad range of clinical indications (McCabe et al., 2010; Ferguson, 2001; Taylor et al., 2006). Even with mild side effect profiles, many patients on these medications still report non-adherence to treatment because of adverse and bothersome side effects (Fortney et al., 2011). Concerns about SSRIs' ability to improve depressive symptoms without adding side effects, such as sexual dysfunction, gastrointestinal upset, and restricted range of emotions, continues to be scrutinized.

Although patients typically claim that they have less emotional pain while on SSRIs than they do during a depressive episode, they also report feeling constrained in the range of emotions they experience, such as the inability to cry or feel enjoyment. When linked to antidepressant treatment, this phenomenon is described as *emotional blunting* or a numbing of emotion (Goodwin et al., 2017). While the mechanisms behind emotional blunting have not yet been determined, a substantial portion of patients taking SSRIs report diminished emotions and an overall new onset of an apathetic disposition (Fisher et al., 2005). Since depression is such a complex disorder – one that is an amalgamation of genetic, neurochemical, neuropsychological, cognitive, and affective domains – it is important to additionally recognize SSRI-induced changes in cognitive and emotional processing that are distinct from depression symptoms.

This study focuses on the emotional side effects of SSRIs that have been anecdotally recorded in the past (Barnhart et al., 2004; Garland & Baerg, 2001; Price et al., 2009).

Currently, the literature on emotional blunting has limited empirical data to support this

phenomenon beyond self-report. To better quantify emotional blunting, the current work will measure differences in accuracy and speed of processing emotional information as a function of SSRI use. Most studies to date have looked at acute administration of SSRIs in healthy subjects when assessing cognitive changes and side effects. To generalize to real-world SSRI use, this study will look at cognitive changes in individuals prescribed SSRIs for depression who are on the drug for at least two months. Using these inclusion criteria, the results of this study will illuminate potential ways to objectively measure emotional blunting in long-term SSRI-users.

1.1 Emotional Blunting

Approximately 20% of patients prescribed an SSRI report new onset of apathy, and 16% describe a loss of ambition after starting the drug (Bolling & Kohlenberg, 2004), though a more recent study showed that 46% of antidepressant users reported emotional blunting (Goodwin et al., 2017). A large international study with 1,340 participants spanning 38 countries asked long-term antidepressant users about adverse effects "as a result of taking the antidepressant." Results revealed that 71% of antidepressant users reported feeling emotionally numbed, 66% reported 'not feeling like myself', and 60% reported a reduction in positive feelings, which are all hallmark components of emotional blunting (Read & Williams, 2018).

Emotional blunting is a wholly subjective phenomenon defined as a reduction in sensitivity in emotional responsiveness to situations where an emotional response would be appropriate, similar to indifference (Price & Goodwin, 2009; Sansone & Sansone, 2010). Over the last few decades, the emotional side effects of SSRI-usage have become more widely recognized and are identified by signs of apathy, a lack of motivation, and a lack of appropriate concern for relationships and interpersonal situations (Price et al., 2009). These altered emotional responses are widespread and affect various domains of a person's life, such as work, school, and

close personal relationships at home (Opbroek et al., 2002; Price et al., 2009). Emotional blunting caused by SSRIs may inhibit individuals from feeling their best because blunting diminishes a person's ability to feel pleasure and can cause a "numbing" of all emotions, including positive ones, such as happiness and joy. Past fMRI research where single doses of antidepressants were administered acutely demonstrated diminished positive emotional responses in SSRI-users (Takahashi et al., 2005). Along with changes in emotional experiences, SSRI-induced emotional blunting often occurs with distinct dose-dependent features. Individuals on higher doses are more likely to experience a behavioral or emotional indifference/apathy (Barnhart et al., 2004). With this said, SSRI-induced emotional blunting is completely reversible by lowering dosage or discontinuing the medication (Barnhart et al., 2004). Although many patients deal with these side effects, little is known about the breadth of SSRI-induced emotional blunting (Garland & Baerg, 2001; Price et al., 2009).

Past research has examined SSRI-induced changes in neural reaction and circuitry. One study looked at changes in amygdala activation before and after 12 weeks of SSRI use. Results showed increased amygdala activity in response to positive stimuli and decreased amygdala activity in response to negative stimuli (Young et al., 2020). Beyond the amygdala, research demonstrates that even just days of SSRI treatment can alter frontal cortex activity in response to emotional stimuli. For example, McCabe and colleagues found that SSRI administration for seven days in healthy controls diminished orbitofrontal and medial frontal neural response to both positive and negative stimuli (McCabe et al., 2010). Meta-analyses examining the role of serotonin in emotional processing have shown that central serotonin availability and transmission modulates the neural response to both positive and aversive stimuli to brain regions known to be involved in reward processing such as the amygdala and frontal lobe (Macoveanu, 2014).

With emotional blunting documented anecdotally through case studies and via newer technology, such as fMRI, looking at simpler ways to measure blunting is pertinent to adequately understanding how SSRI-induced neural circuitry changes impact overall functioning. By assessing cognitive differences in emotional processing, it would be possible to have a more complete understanding of SSRIs' effects on the mind as well as provide a quick and cost-effective way to test for the presence of emotional blunting, track it over time, and determine a risk/benefit analysis of dose titration in patients taking this medication. To assess for blunting during their appointments, patients could easily complete brief cognitive tasks, the same way they update their demographic information or fill out self-report measures of depression. Likewise, by recording baselines and performing serial follow-up assessments, cognitive responses to emotional stimuli could be tracked over time and assessed alongside dosage and brand changes, much like the way depression symptoms are tracked using self-report measures such as the Beck Depression Inventory (Beck et al., 1996). For example, if a person reports new onset feelings of distance from their romantic partner, a prescriber could refer to previous cognitive evaluations and compare test data to the patient's current cognitive performance. This process would emulate the way neuropsychologists track changes in memory over time for patients with neurodegenerative diseases such as dementia or epilepsy (Amarigilio et al., 2015; Sen et al., 2018). Thus, cognitive assessment would allow for a preventative approach to emotional blunting, possibly even before the patient is aware of its occurrence, allowing prescribers to connect social disruptions to potential emotional blunting.

1.2 Accurate Measurement of Emotions

Past research demonstrates that consciously reporting "how we are feeling" may not be an accurate way of assessing emotions, as it may alter autonomic system processes that produce

authentic emotional responses. Given this concern, self-report is not ideal in assessing emotions as it can alter the underlying biological aspects of emotion (Scherer, 2005; Kassam & Mendes, 2013). Previous attempts to steer away from self-report when acquiring data on emotions have been made for many decades. Past work addressing apathy and depression used caregiver report instead of self-report, as these clinical syndromes can inherently cause reduced awareness of change (Zahdone & Tremont, 2012) though caregiver report still remains subjective. Previous attempts to steer away from self-report when acquiring data on emotions have been made to remove subjective confounds altogether. For example, relationships between viewing emotional pictures or words and changes in cardiovascular and electrodermal responses are well documented (Bernat et al., 2001; Lang et al., 1993). Using cognitive measures instead of self-report to study emotion may provide more accurate data, as performance on cognitive tasks is freer from self-awareness or conscious rumination (Kassam & Mendes, 2013). For example, relationships between viewing emotional pictures and changes in cardiovascular and electrodermal responses are well documented (Bradley et al., 1996; Bernat et al., 2006). Similarly, past research has looked at facial muscle movement to assess facial expressions while viewing emotional pictures to determine emotional responsiveness (Lang et al., 1993).

Beyond lacking the ability to tap into biological aspects of emotions, self-report on emotional expressivity, intensity, and appropriateness is not reliable because many patients are not consciously aware of their emotional state. Regarding SSRI-induced blunting, previous research has documented the insidious onset of emotional blunting and how it often goes unnoticed, making the use of objective measures, such as reaction times or response inhibition on cognitive tasks, beneficial in detecting emotional blunting and even more necessary (Price et al., 2009). Some studies have demonstrated that SSRI-induced emotional blunting often coincides

with reduced insight, particularly in children and adolescents (Reinblatt & Riddle, 2006). The emergence of SSRI-induced emotional blunting may also be slightly delayed, making it more difficult to tie the new blunted affect to the medication itself (Reinblatt & Riddle, 2006).

1.3 Selective Serotonin Reuptake Inhibitors

SSRIs are a class of antidepressants that inhibit 60-80% of serotonin uptake to efficaciously treat both depressive and anxiety disorders (Alarcon & Prekorn, 2004). The brands currently available for prescription in the US include Prozac (fluoxetine), Celexa (citalopram), Lexapro (escitalopram), Paxil (paroxetine), and Zoloft (sertraline). Abnormal serotonin (5-HT) systems in patients with psychiatric disorders have been documented for decades, making serotonin the crucial target of pharmacological treatment (Biver et al., 1997). Using central serotonin agonism, these medications balance low levels of free-flowing serotonin in individuals with psychiatric symptoms, as low levels of unbound serotonin are linked to depression and anxiety (Macaluso & Preskorn, 2019). SSRIs and other drugs affecting serotonergic transmission are effective for the treatment of depression, as they work to keep more serotonin freely lingering in the blood and block uptake by neurons. While other antidepressants, such as tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs), exist, SSRIs are preferred by prescribers as they have a reliable dose-response curve for adverse effects, making it easy to manage side effects by titration.

1.4 Physical Side Effects of SSRIs

While the current investigation focuses on emotional side effects of SSRI use, it is important to note that SSRIs are linked to physical side effects as well. For instance, 41% of adult patients taking SSRIs for depression reported at least one adverse physical side effect of the drug, such as sleep and gastrointestinal disturbances, nonspecific malaise, and appetite/weight change (Rascati

et al., 2001). A 2009 study of 700 SSRI-users found that sleepiness and weight gain were the most common physical symptoms reported in over 100 users, with dry mouth, nausea, tremors, and dizziness also present (Cascade et al., 2009).

1.5 Sexual Side Effects of SSRIs

Anecdotal data also show that SSRI-use can disrupt many parts of sexual response, including arousal, excitement, and orgasm (Balon, 2006). Disruption in normal sexual functioning, for example, a low libido or inability/difficulty to orgasm, is one of the most commonly reported sexual side effects of SSRI usage (Balon, 2006). One study revealed that sexual dysfunction was the most common side effect of SSRI use, above and beyond physical side effects (Cascade et al., 2009). In fact, it is believed that sexual dysfunction affects as many as 80% of SSRI-users (Gitlin, 1994; Rosen et al., 1999). Unfortunately, SSRI-users with sexual dysfunction often have co-occurring emotional blunting. One study found that 80% of SSRI-users with sexual dysfunction side effects also reported a dulling of emotions following treatment (Opbroek et al., 2002). Similarly, a study on SSRI use and physical attraction found that SSRI-users with combined low libido and difficulties with orgasm were most susceptible to lowered attraction (Tocco & Brumbaugh, 2018). Based on this high percentage of co-occurrence, it is possible that the same brain regions affect sexual and emotional functioning with overlapping neuronal pathways; therefore, SSRI-users who exhibit sexual dysfunction may have a greater vulnerability for a dulled emotional profile. It is likely that the neurological response is altered after being exposed to SSRIs, and emotional blunting may result from this change.

1.6 Social Side Effects of SSRIs

Past studies have targeted the social implications of emotional blunting. Examining young patients, Garland and Baerg (2001) found many physicians reported that after six to eight

weeks of SSRI treatment, their patients no longer cared about social interactions or consequences for bad behavior. Other qualitative work reports SSRI-users' reduced enjoyment of social interactions, decreased love/affection towards others, and decreased attraction to their current romantic partner (Price et al., 2009). Some SSRI-users demonstrated detachment during social situations, including those with partners and children, and some also cared less about themselves after starting their medication. Other social effects of SSRIs include reduced care or love towards family members and lower sympathy and empathy for others in general (Price et al., 2009). SSRI-induced emotional blunting can be so severe in some patients that it produces flat affect with a mask-like appearance similar to what is seen in Parkinson's disease (Garland & Baerg, 2001).

While most social side effects of SSRI use are anecdotal, one study recently found that SSRI-users had lower levels of attraction to novel individuals than to people not on the medication (Tocco & Brumbaugh, 2018). This finding empirically demonstrates that emotional blunting socially impacts the way a person taking SSRIs views others. Although SSRIs can have a significant benefit for mental health, it is important to recognize that they can also cause a restricted emotional range, which may be harmful for day-to-day functioning. If SSRIs negatively impact one's ability to form meaningful social connections due to blunting, then SSRIs may potentially create *new* problems related to social isolation or disinterest. Because blunting occurs secondary to SSRI use, it is possible that pleasure centers in the brain are altered and obstruct the patient's ability to notice negative impacts on their social relationships or even from seeing the benefits of initiating a new relationship. Past research has shown that relationship initiation requires "bold and direct action" (Cameron et al., 2013), but without a full

range of emotions, SSRI-users may lack the initiative to act, potentially leading to lessened ability to seek out needed support systems (Uchino et al., 1996).

1.7 Classification of Apathy

While the current study will look at cognitive changes associated with SSRI-induced emotional blunting, it is important to note that emotional blunting has similar features to apathy. Apathy is a common public health problem that is particularly prevalent in older adults. Some studies have documented that approximately 49% of individuals over the age of 77 report symptoms of apathy (Grool et al., 2014). Apathy is associated with a surplus of negative correlates and consequences such as poor daily functioning, decreased quality of life, caregiver burden, and poor treatment compliance (Yaeger & Hyer, 2008; Pluck & Brown, 2002). This phenomenon has been well studied and recorded in conditions such as mild cognitive impairment (MCI), Alzheimer's Disease (AD), Parkinson's Disease (PD), schizophrenia, and depression, all of which are diseases that impact the prefrontal cortex-limbic system circuitry (Montoya-Murillo, et al., 2019). Apathy was first characterized as a complex neurobehavioral syndrome with a lack of motivation that affects behavior, emotions, and cognition that is not otherwise attributable to psychiatric disease or alterations in conscious awareness (Marin, 1991). Marin postulated that accurate diagnosis of apathy would need to assess action initiation, emotion, intellectual curiosity, and self-awareness (Marin 1991; Murphy, 2000). Levy and Dubois attempted to define apathy as a quantitative reduction in self-generated voluntary and purposeful behavior by characterizing three main areas of disruption that are caused by apathy and their subsequent pathology. Their research considered apathy to be a multidimensional syndrome, with disruption in emotional and cognitive processing and a deficit in 'auto-activation' (Levy & Dubois, 2006). The disruption in emotional-affective processing refers to the inability to link

emotional signals to forthcoming behavior and is thought to be caused by lesions in the orbital-medial prefrontal cortex or limbic territories such as the ventral striatum of the basal ganglia. Cognitive processing disruptions due to apathy encompass difficulty elaborating on plans of actions for future behavior and are linked to lesions in the dorsolateral prefrontal cortex and the dorsal caudate nucleus of the basal ganglia. The deficit in auto-activation is the inability to self-initiate thoughts and actions with spared ability to generate externally motivated behavior and is known as the most severe aspect of apathy (Levy & Dubois, 2006). Deficits in auto-activation are seen when bilateral lesions in the limbic system, particularly the globus pallidus, result in diminished signal to the frontal cortex. While apathy is well-defined, researched, and correlated with structural brain regions, a potential source of confusion presents when one attempts to distinguish apathy from depression, given their similar clinical presentations.

1.8 Distinction between Apathy and Depression

According to the Diagnostic and Statistical Manual of Mental Health Disorders (DSM-5), depressive disorders are defined by the presence of sad mood and significant cognitive and somatic changes that cause functional impairment. The World Health Organization defines depression as a syndrome with permanent abnormal mood for at least two consecutive weeks and a marked diminished interest or pleasure and decreased energy associated with at least one of the following: loss of confidence, excessive guilt, recurrent thoughts of death, poor concentration, sleep disturbance, and change in appetite/weight. Apathy is not a clinical criterion for depression, but it is often present in individuals with depression (Marin et al., 1993). While apathy and depression both affect similar target areas in the brain, apathy is known to occur in the absence of depression, such as MCI, AD, and PD, rather than from altered affect and correlates with

distinct locations of lesions in the brain (Anderson et al., 1999). Overall, apathy and depression may coexist, but they are also clinically *independent* syndromes.

When apathy occurs in the context of depression, it is best described as decreased motivation and difficulty initiating thoughts, emotions, and goal-directed behavior, which is associated with disruptions in the frontal-striatal circuitry of the brain (Marin, 1990). Depression is characterized by dysphoric symptoms (e.g., sadness, guilt, and helplessness) not seen in individuals with apathy alone. Depressed individuals also have high rates of negative self-criticism. In contrast, apathy is characterized by a lack of emotional responses and a lack of concern in general (Marin, 1990; Marin, 1997). Both depression and apathy can lead to loss of interest, but the underlying etiology is different. In depression, loss of interest is due to feelings of despair, pessimism, and hopelessness. In apathy, loss of interest is due to decreased motivation (Marin, 1997). The theory of separate constructs is further supported based on treatment differences: depression is treated with SSRIs while apathy is not, as SSRIs can exacerbate apathy, particularly in older adults (Wongpakaran et al., 2006).

Often, apathy occurs as a symptom of depression, but true apathy and depression are clinically independent from one another, which is why emotional blunting in individuals who adequately respond to SSRI treatment can still occur (Levy & Czernecki, 2006). While apathy and depression share many overlapping symptoms like blunted affect, lowered initiation of goal-directed behaviors, and a lack of engagement, many symptoms of depression are exclusive to depression alone such as suicidal ideation, crying, changes in sleep, and hopelessness (Marin, 1990; Landes et al., 2001).

Pure apathy is a commonly seen neuropsychiatric symptom of many neurological diseases, which is further evidence that apathy is an independent construct and occurs in the

absence of depression. For example, many patients with progressive supranuclear palsy (PSP) and frontotemporal dementia (FTD) rarely meet criteria for depression but often present with apathy (Marin et al., 1994; Yeager & Hyer, 2008). Forty percent of patients with MCI and AD also exhibit apathy whereas only twenty percent of patients with MCI or AD exhibit depression (Apostolova & Cummings, 2008). Similarly, meta-analyses show that apathy occurs in approximately 40% of all Parkinson's disease patients (den Brok et al., 2015). Like FTD and PSP, Parkinson's disease-related apathy likely occurs secondary to disruptions in the frontal-subcortical circuitry (den Brok et al., 2015). Some studies have attempted to clarify the differences in frontal circuitry deficits via neuropsychological evaluation. For example, a 2012 study of 90 patients revealed that depression alone was associated with poor set-shifting. This study also revealed that apathy, not depression, was associated with increased functional impairment (Zahodne & Tremont, 2012). Similarly, research looking at cognitive impairment in Alzheimer's disease showed that self-report measures of apathy and depression often correlate due to overlapping symptoms of loss of interest, psychomotor slowing, and a lack of energy (Marin et al., 1993); therefore, separate scales to address apathy independently were created. Currently, psychometric support exists for the use of self-report scales that measure apathy independently, with validated questionnaires and well-established cut-off scores (Marin, 1991). Multiple scales also exist to assess apathy as a distinct clinical presentation (Radakovic & Abrahams, 2014; Robert et al., 2002; Sockeel, 2006).

The measurement of apathy as a separate construct began in the 1990s for neurological populations, though the first self-report questionnaire for SSRI-induced apathy was created 20 years later (Price et al., 2012). The Questionnaire on the Emotional Side-effects of Antidepressants (OQuESA; Price et al., 2012) specifically targets the emotional components of

apathy like blunted affect and poor social engagement, with an index to determine how much people believe that the SSRI is responsible for their current state. With apathy and depression viewed as distinct and separate constructs, SSRI-induced emotional blunting in treatment responders (i.e., those who no longer feel depressed) should be assessed in the absence of depression. The current study seeks to look at new onset emotional blunting via the OQuESA after long-term SSRI use to ensure that changes in emotional processing are exclusively due to SSRI-induced changes and not to lingering symptoms of depression.

While apathy in depression may look similar to SSRI-induced emotional blunting, true emotional blunting only occurs *after* SSRI administration and would not be seen in a depressed patient not on medication (Plowden, 2019). This unique difference in timing allows prescribers to better distinguish between depression and a new onset apathy syndrome. Many individuals who have SSRI-induced apathy will initially get better, as the SSRI is effective in treating the depression, but later deteriorate due to the side effect of apathy (Plowden, 2019). Given the overlap in symptoms of depression and new onset blunting, this study will look only at treatment responders who no longer endorse depressive symptoms. It would be nearly impossible to determine if changes in cognition and behavior were due to depression or SSRI-induced apathy prior to successful recovery from depression. By eliminating individuals with continued depressive symptoms and only looking at non-depressed treatment responders, this study will be able to draw conclusions about pure SSRI-induced apathy without having to consider confounding overlap with lingering depression. The impact of SSRI-induced apathy on processing emotional information will be able to be examined, similar to the way past research has looked at the effect of neurological disease-induced apathy on cognition.

1.9 Social Support and Mental Health

In recent decades, many studies have cited the importance of social support and close relationships in individuals with mental illness. Social support involves positive interactions between people who are perceived as helpful and provide psychological advantages (Harandi et al., 2017). Social support is known to improve quality of life, aid with mental illness, and be protective from the effects of stress (Turner & Brown, 2010). Social support is also seen as one of the top three most important constructs in mental health research (Veiel & Baumann, 2016). Lack of perceived social support is directly related to depressive symptoms, especially later in life (Berkman & Glass, 2000). More recent research shows that the relationship between social support and depression is strong, as social support can aid in recovery after depression has already occurred, especially for women and older adults (Harandi et al., 2017; Grey et al., 2020). Beyond depression, social support is inversely related to anxiety, loneliness, irritability, and poor sleep quality (Grey et al., 2020; Roohafza et al., 2014). With decades of research highlighting the importance of social support in the prevention and recovery of mental illness, ensuring that treatments, such as SSRIs, do not perpetuate social distance or increase the risk of individuals withdrawing from their social networks due to emotional blunting is essential. Social support is an integral protective factor against mental illness that prescribers need to ensure is not altered or damaged by SSRI-induced emotional blunting.

1.10 Neurological Biomarkers of Blunting

Initial anecdotal reports of emotional blunting from SSRI-users prompted fMRI research to capture SSRIs' effects on the brain, as neuroimaging biomarkers of emotional blunting could help better predict treatment response, in turn, helping clinicians implement changes in treatment for better patient outcomes (Spies e al., 2017). Techniques, such as fMRI, have helped

researchers determine differences in brain activity based on the amount of oxygen use in specific brain regions. Functional magnetic resonance imaging is an expensive and time-consuming procedure, though it could hypothetically allow prescribers to see activation changes of emotion regulating areas, aiding in the assessment of emotional blunting. For example, if a brain region uses a steady and high amount of oxygen from the blood, that region becomes highly activated. One study assessed the emotional discrimination abilities of patients with Major Depressive Disorder (MDD), examining their brain activity prior to SSRI treatment and then, again, after two and four weeks of SSRI escitalopram (Lexapro) administration. Overall, deactivation of the precuneus and posterior cingulate cortex, areas known for processing and detecting negative information, resulted in lower levels of depression after two weeks of treatment (Spies et al., 2017). Similarly, a study of patients with MDD showed deficits in managing cognitive interference when distractors had negative emotional valence (Fales et al., 2009), suggesting that people with depression are drawn to negatively charged information. When compared to MDD patients without SSRI treatment, SSRI-users had a significant increase in activation of the dorsolateral prefrontal cortex (DLPFC), above and beyond the depressed group not on SSRIs. They also showed a reduction of amygdala activity in response to photos of fearful facial expressions (Fales et al., 2009). These results suggest that antidepressant therapy may actually improve recruitment of the DLPFC during performance of emotional interference tasks, thus leveling out the negative bias often seen in depression.

Some studies have even tested SSRI use independent of depression by putting healthy control subjects on an SSRI to truly distinguish emotional blunting that is merely induced by an SSRI and not part of the originally-treated condition of depression. McCabe and colleagues (2010) assessed neural responses to rewarding (pleasant sight and/or flavor) and aversive stimuli

(unpleasant sight and/or flavor) after one week of SSRI citalopram (Celexa) treatment. Results showed that citalopram reduced activation to the pleasant stimuli in the ventral striatum and the ventral medial/orbitofrontal cortex. Furthermore, citalopram also decreased neural responses to aversive stimuli in key "punishment" brain areas such as the lateral orbitofrontal cortex. Thus, SSRI treatment decreases neural processing of both rewarding and aversive stimuli, which can be problematic if a person is also experiencing SSRI-induced decreased motivation and anhedonia (McCabe et al., 2010). A comparable randomized control trial of depressed patients using citalopram or reboxetine (norepinephrine reuptake inhibitor-NaRI) found that, overall, these antidepressants decreased the recognition of negative emotions (Tranter et al., 2009).

While Tranter and colleagues (2009) found that both norepinephrine and serotonin affected emotional recognition, other studies looking at dopaminergic and serotonergic manipulation indicated that healthy controls had altered neural emotional responses to unpleasant pictures when given an SSRI or D2 antagonist (Takahashi et al., 2005). Functional magnetic resonance imaging (fMRI) revealed that acute administration of a therapeutic dose of dopamine (DA) D2 antagonists and fluvoxamine (Luvox-SSRI) had modulatory effects on emotional processing. Specifically, the amygdaloid-hippocampal regions, orbitofrontal cortex, basal ganglia, and insula showed reduced activation when subjects viewed unpleasant images (Takahashi et al., 2005). Unlike the DA D2 antagonist, SSRI treatment produced greater activation only in the temporal cortex and parietal cortex, and not in the frontal cortex, suggesting that SSRI use may primarily affect the frontal lobe, which is known to be related to emotional processing and personality (Takahashi et al., 2005). Although both DA D2 antagonist and SSRI treatment resulted in common inhibitory effects on amygdaloid – hippocampal regions, the different patterns found in the prefrontal cortex strongly confirm that SSRI use uniquely

affects the brain. This pattern of inhibition on prefrontal cortex occurred even when subjective ratings of affective pictures did not produce a significant difference between groups, confirming that self-report of emotion is indeed unreliable and uncorrelated to biological changes such as neuronal activation (Takahashi et al., 2005). Acute administration of SSRIs reduced activity in the amygdala, suggesting the brain's primary emotion center was being down-regulated or "blunted." In addition, SSRI use did not raise activity in the frontal cortex, which is a region likely requisite for full emotional processing of information. It is known that depression causes hypoactivity in left frontal areas and hyperactivity in right frontal areas (Walsh et al., 2010); therefore, changes in frontal lobe processing would be expected to alter with SSRI usage to combat depression.

While most of the aforementioned work assessed differences between SSRIs and other drugs in healthy controls, functional neuroimaging emotion research has also been done to assess whether neural markers of early emotional processing changes predict later clinical response in depression (Godlewska et al., 2016). At baseline, depressed patients showed greater activation to fearful faces versus happy faces than controls in the insula and dorsal anterior cingulate. Furthermore, "treatment responders" had a greater reduction in neural activity to fearful versus happy facial expressions in a multitude of brain regions including the anterior cingulate, insula, amygdala, and thalamus, suggesting that these areas were no longer hyperactivated by negative emotional information. Overall, these longitudinal results support the hypothesis that changes in emotional processing occur early on in antidepressant usage (Godlewska et al., 2016) and parallel Fales' (2009) findings of changes in emotional processing after only two weeks of SSRI administration.

Beyond looking at specific regions of the brain, research has examined broader hemispheric differences during processing of emotional information. Walsh and colleagues (2010) assessed SSRI-users that ranged from never depressed, previously depressed, and currently depressed/using SSRIs (including "responders" whose depression improved post SSRI versus treatment resistant "non-responders"). Each group viewed both positively- and negatively-valenced words to determine if SSRI use caused hemispheric differences in activation. SSRI responders and never-depressed participants were similar in their left hemispheric lateralization when evaluating emotional words. On the other hand, SSRI non-responders showed a relative shift towards right hemisphere processing of negative words and a strong bias toward negative evaluation of words in the right hemisphere. In sum, patients still having symptoms of depression had different hemispheric activation than patients who responded well to the SSRI. It is possible that non-responders to SSRI administration experience emotional blunting, which prevents them from feeling better, contrasting with the notion that non-responders are truly treatment-resistant. The current work seeks to examine only SSRI treatment responders in order to distinctly study SSRI-induced emotional blunting without persistent depressive symptoms. Non-responders were omitted because they leave too much open to interpretation, as SSRI-induced emotional blunting has substantial overlap with depressive apathy.

1.11 SSRI Research in Anxiety Disorders

While SSRIs are primarily used to treat MDD, they have also been clinically indicated in anxiety disorders, such as panic disorder, social phobia, post-traumatic stress disorder, generalized anxiety disorder, and obsessive–compulsive disorder. These disorders do not have the same rate of anhedonia and apathy as MDD; therefore, examining SSRI use in these

populations allows researchers to view anhedonia and SSRI-induced emotional blunting as two separate and distinct constructs (Burghardt and Bauer, 2013). To investigate the effects of SSRIs in the brain, Burghardt and Bauer measured behavioral effects in animals subjected to Pavlovian fear conditioning. To demonstrate how SSRIs affect the functioning of specific brain regions, including the amygdala, nucleus bed of the stria terminalis, and hippocampus during fear, Burghardt and Bauer (2013) acutely administered an SSRI. Neural activity in the extended amygdala and hippocampus showed enhanced activation from cued fear conditioning. This effect additionally impaired context-dependent fear conditioning (Burghardt & Bauer, 2013). Furthermore, the effects of chronic SSRI treatment on fear conditioning in rodents revealed that down regulation of N-methyl-D-aspartate (NMDA) receptors in the amygdala and hippocampus may mediate impairments in fear learning and memory (Burghardt & Bauer, 2013). These results suggest that long-term SSRI use in humans potentially causes differences in cognitive processing of fear and other emotions.

1.12 Cognitive Effects of Depression

To date, many studies have highlighted the cognitive changes associated with pathophysiology, symptoms, and treatment of depression. Cognitive symptoms of major depressive disorder include abnormal emotion processing and altered cognitive function, including executive dysfunction, which can be seen on fMRI (Fales et al., 2009). In terms of emotional processing specifically, depression is associated with a wide scope of negative biases. For example, depressed individuals are more likely to selectively recall negative, self-related emotional information in memory tasks and demonstrate negative biases in the perception of social signals such as emotional facial expressions (Godlewska et al., 2016). Hypoactivity in left frontal and right posterior areas and hyperactivity in right frontal areas are also linked to

depression. Vulnerability to depression is linked to specific neurophysiological characteristics, including greater right-hemisphere (RH) relative to left-hemisphere (LH) activity. This atypical pattern of hemispheric asymmetry seems to be a stable trait present in both those at risk for and those in remission from depression (Walsh et al., 2010). Past work in depressed samples also recorded altered recognition of facial expressions, likely due to underlying cognitive changes and increased sensitivity to subtle social cues (Harkness et al., 2005; Persad & Polivy, 1993). One study on SSRI use and emotional processing showed that sub-chronic SSRI exposure decreased accuracy of facial expression recognition (Harmer et al., 2004). Depression is also associated with executive dysfunction especially in domains of psychomotor speeds and inhibition when compared to their non-depressed counterparts (Bennabi et al., 2013; Channon & Green, 1999). While most research has focused on changes in the amygdala and prefrontal cortex, neurobiological models of depression also emphasize alterations in language centers (Merens et al., 2007). For example, some studies have discovered that depressed individuals demonstrate reduced semantic fluency (Fossati et al., 2003; Schmid & Hammer, 2013).

To gauge the depth and breadth of depression on cognition, some researchers use a method of tryptophan depletion which is thought to decrease neuronal serotonin to mimic the "depressed brain" (Neumeister, 2003). Tryptophan depletion reveals slowed responses to positive verbal stimuli in an affective go-no go task (Murphy et al., 2002), reduced memory for positive affective information (Klaassen et al., 2002), and increased Stroop interference for negative stimuli (Evers et al., 2006). These effects perpetuate a negative skew on a cognitive level and may be similar to an SSRI blunted brain, as depression apathy and SSRI-induced blunting have such a high level of overlap.

With cognitive changes in depression well documented, it is crucial to switch gears and begin looking at cognitive changes in patients who not only take SSRIs, but also report emotional blunting associated with their prescription use. Research on cognitive changes in depression proves fMRI's ability to elucidate changes in emotional processing, but fMRI is not typically used in clinical practice. At present, insurance companies do not cover the cost of fMRI to establish cognitive changes secondary to depression. This type of testing is expensive and cumbersome, placing a high burden on the patient. Without the use of fMRI in depressed patients, there is little hope that such a test would be offered to SSRI-users who report emotional blunting; therefore, finding alternative ways to assess emotional processing and cognitive changes associated with SSRI use is warranted.

1.13 Past Research in Emotional Processing with SSRI Use

Limited research exists on the direct link between cognitive processing of emotionally charged information and SSRI use. Though limited, research has shown that SSRI use does indeed alter the way the brain processes emotional information, but these studies largely focus on acute SSRI administration (Fales et al., 2009; Godlewska et al., 2016). One study found that healthy subjects on citalopram (an SSRI) for one week had a reduced ability to identify facial expressions of anger and fear when compared to their placebo counterparts (Harmer et al., 2004). Likewise, one week of citalopram resulted in decreased startle response for negative affective images.

Beyond short-term SSRI use, little research has assessed altered processing of emotional information in chronic SSRI use for depression. One study on SSRI use and emotional processing showed that sub-chronic SSRI exposure decreased accuracy of facial expression recognition (Harmer et al., 2004). Past work in depressed samples recorded altered recognition of

facial expressions, likely due to underlying cognitive changes and increased sensitivity to subtle social cues (Harkness et al., 2005; Persad & Polivy, 1993), which may be similar to the effects on SSRI-users with emotional blunting given the overlap in clinical presentation.

Along with facial recognition accuracy, there is longstanding literature that supports a phenomenon known as "emotional interference." Emotional interference is characterized by attentional changes when individuals are presented emotional stimuli that resonate closely with a person. For example, individuals with PTSD often show slowed reaction times when presented with words closely associated with their trauma (Vythilingam et al., 2007). Comparably, multiple studies demonstrate that depressed patients have slower response times to negatively valenced words than to positive or neutral words, above and beyond their control counterparts (Mitterschiffthaler et al., 2008; Ros et al., 2021). Hence, emotional interference appears to be related to the thematic relevance of the personally experienced event. Since SSRI-induced emotional blunting results in a distance from all emotions and is associated with pulling away from loved ones and difficulty with social interactions (Garland & Baerg, 2001), these individuals may "pull away" and distance themselves from all emotionally charged information, resulting in changes in processing speed. While these studies addressed differences in emotional processing associated with psychopathology, little research on emotional processing changes stemming from SSRIs exists.

1.14 The Current Study

This study seeks to build upon past research by investigating emotional processing changes in long-term SSRI-users to determine if SSRI-users who specifically report varying levels of emotional blunting and/or sexual dysfunction demonstrate differences in emotional processing than long-term SSRI-users without these difficulties. By focusing on cognitive

changes, the current study attempts to find an objective way to quantify emotional blunting. If SSRI-induced emotional blunting alters cognitive performance on tasks that contain emotionally charged information, prescribers could rely on differences in cognitive performance over time to objectively capture blunting without needing to rely on a patient's awareness and ability to detect its presence. Assessing emotional blunting by measuring cognitive changes would also allow for *preventative* care instead of waiting for the side effect of emotional blunting to emerge. This study would be the first of its kind, assessing the effects of emotional blunting beyond anecdotal report and considering that emotional blunting can also alter emotional processing in patients on SSRIs. This information would foster a more in-depth understanding of how SSRI-induced blunting impacts emotional processing and the social implications this change can have on a person's life.

This study also seeks to fill gaps in the current literature by examining long-term SSRI-users. Previous work on emotional blunting, including fMRI studies, has tested SSRI effects in healthy volunteers who receive an SSRI only once or for a brief period of time (minutes or weeks rather than the typical months or years of treatment). The novel approach used here of studying SSRI-users who have been on medication for at least two months to treat depression is more applicable to real-world cases, as SSRIs are only prescribed for a psychiatric condition and not to healthy individuals. Furthermore, this study seeks to study the relationship between emotional blunting and sexual dysfunction given that sexual dysfunction is one of the most common and pressing side effects of SSRI use. One study noted the correlation between SSRI-induced sexual dysfunction and emotional blunting (Opbroek et al., 2002), but, to date, there is limited research, and the correlation has only been established based on case study. An experimental design that allows for the evaluation of cognitive differences in long-term SSRI-

users with and without emotional blunting *and* with and without sexual dysfunction will allow for generalizability of findings, provide a potential avenue for detection of this insidious side effect, and build on the limited empirical work addressing SSRI-induced emotional blunting.

1.15 Current Aims and Hypotheses

This study aimed to investigate the effects of long-term SSRI use on emotional processing of information in treatment responders. The present study has the following aims:

Aim 1. To determine if long-term SSRI-users show differences in their cognition when processing emotional information.

Hypothesis 1A. I expected that long-term SSRI-users would have lower accuracy in recognizing emotions than controls, as determined by the Affect Naming task.

Hypothesis 1B. I predicted that long-term SSRI-users would show smaller differences in reaction times based on valence of words (positive, neutral, and negative) than controls, as they are more likely to feel blunted and feel distanced from all emotions. I hypothesized that there would be greater differences between reaction time for positive and neutral words or negative and neutral words in control subjects when compared to SSRI-users, as they may feel more aligned with emotional content. This will be determined by their reaction times on the Emotional Stroop Task.

Aim 2. To determine if long-term SSRI-users who endorse emotional blunting (as determined by the OQUeSA) show greater differences in cognitive processing of emotional information than long-term SSRI-users who do not endorse emotional blunting.

Hypothesis 2A: I hypothesized that long-term SSRI-users who report emotional blunting would have poorer accuracy in recognizing emotions than long-term SSRI-users who subjectively deny emotional blunting, as determined by the Affect Naming task.

Hypothesis 2B: I hypothesized that long-term SSRI-users who subjectively endorse emotional blunting would show less variability in reaction times based on emotional valence of words (positive, neutral, and negative) than long-term SSRI-users who do not report emotional blunting, as they are more likely to feel blunted and feel distanced from all emotions. This will be determined by their reaction times on the Emotional Stroop Task.

Aim 3. To determine if SSRI-users who attribute their blunting specifically to their antidepressant process emotional information differently.

Hypothesis 3A. I hypothesized that long-term SSRI-users who attribute their blunting to their antidepressant would have poorer accuracy on recognizing facial expressions than long-term SSRI-users who do not attribute their blunting to SSRI use, as determined by the Affect Naming task.

Hypothesis 3B. I hypothesized that long-term SSRI-users who attribute their blunting to their antidepressant would show less variability in reaction time based on emotional valence of words (positive, neutral, and negative) than long-term SSRI-users who do not attribute their blunting to SSRI use. This will be determined by their reaction times on the Emotional Stroop Task.

Aim 4. To determine if long-term SSRI-users who report sexual dysfunction as a side effect are more likely to experience emotional blunting.

Hypothesis 4A: I hypothesized that long-term SSRI-users who endorse sexual dysfunction (low libido and/or difficultly/inability to orgasm) would have higher levels of emotional blunting than long-term SSRI-users who do not endorse any sexual dysfunction side effects, as determined by the OQUeSA.

Aim 5. To determine whether long-term SSRI-users who endorse sexual dysfunction are at an increased risk of inaccurately processing emotional information.

Hypothesis 5A: I hypothesized that SSRI-users who report sexual dysfunction side effects (low libido and/or difficulty/inability to orgasm) would have poorer accuracy in recognizing emotions than long-term SSRI-users who do not report sexual dysfunction side effects due to higher levels of emotional blunting, as determine by the Affect Naming task.

Hypothesis 5B: I hypothesized that long-term SSRI-users who subjectively endorse sexual dysfunction would show less variability in reaction times based on valence of words (positive, neutral, and negative) than long-term SSRI-users who do not report sexual dysfunction due to higher levels of emotional blunting. This will be determined by their reaction times on the Emotional Stroop Task.

2. Methods

2.1 Study Design

Power Analysis

Power analysis was conducted using G*Power (Faul et al., 2007). Estimation of sample size was based on a general linear model with between subject factors. The effect size for the main outcome measures in this sample was expected to be small to medium, based on the relatively low level of psychiatric severity and cognitive difficulties expected to be detected in the sample. Based on this power analysis, a sample size of 64 participants per group was adequate to detect a small to medium effect size with 0.80 power at the .05 level of significance for the primary outcome measures.

Recruitment

This study was approved by the Institutional Review Board of Queens College, CUNY. Participants were recruited via Prolific, an online research platform that has a built-in database of registered SSRI-users. Participants were required to be at least 18 years old, live in the United States, have access to a computer, and have English proficiency. Mobile viewing of the survey was disabled in order to standardize administration of the Emotional Stroop Task. For SSRI-users, individuals were required to be on the medication for a minimum of two months, to establish what I defined as "long-term use." Participants were excluded if they reported using any psychiatric medication other than an SSRI, such as benzodiazepines, serotonin-norepinephrine reuptake inhibitors (SNRIs), or antipsychotic medication. Due to the overlap in symptoms between SSRI-induced emotional blunting and depression-induced apathy, participants who met criteria for depression (BDI-II > 13) were excluded from the main results in order to determine if the effects were truly from new onset blunting. Individuals who met criteria for anxiety (BAI > 15) were also excluded due to an exceptionally high comorbidity rate (~50%) between anxiety disorders and depressive disorders and because individuals with anxiety are known to have altered emotional processing (Brown et al., 2001). Individuals who endorsed color blindness were also excluded, as they would not be able to participate in the Emotional Stroop Task. Participants were compensated $2.85 for their participation. Participants consented online and confirmed they were a human using reCAPTCHA. They then completed the Beck Depression Inventory, the Beck Anxiety Inventory, a demographics survey, and the OQuESA. Individuals on SSRIs, a category that was preselected on Prolific, also filled out the SSRI usage form. Following self-report measures, all participants completed the Emotional Stroop Task and viewed the Advanced Clinical Solutions Affect Naming task. Two attention check questions were included in the survey.

2.2 Participants

Two hundred and twenty-seven participants (118 SSRI-users and 109 control subjects) participated online. Of those 227 subjects, 105 scored above the cut off for depression (BDI-II > 13) and were omitted from the reported analyses. While this rate of depression (almost 50%) is far higher than national averages, data were collected in October of 2020 during the COVID pandemic which may partially explain general mental health during this time. Thus, the following analyses are based only on the 122 adults who screened as non-depressed.

Final Sample

In the final sample of 122 adults, 50% (*n*=61) reported current SSRI use and 50% (*n*=61) were controls (see Table 1). Overall, the sample mean age was 35.18 years (*SD* = 13.48). Most participants were white (77.0%, *n*=94), 9.8% were Asian (*n*= 12), 7.4% were African American (*n*= 9), 2.5% were American Indian/Native Alaskan (*n*= 2), and 4.1% identified as 'other' (*n*= 5). The majority of participants were heterosexual (81.15%, *n*=99), with 6.55% identifying as gay (*n*= 8), 8.2% identifying as bisexual (*n*= 10), and 4.1% identifying as 'other' (*n*= 5). Seventy-eight people (63.9%) reported being in a romantic relationship. Most reported a household income of $30,000 or less (21.3%, *n*= 26), with 15.25% stating their annual household income as $30,000-$50,000 (*n*= 19), 18.85% in the $50,000-$70,000 range (*n*= 23), 13.95% in the $70,000-$90,000 range (*n*= 17), 14.75% in the $90,000-$125,000 range (*n*= 18), 11.5% in the $125,000-$175,000 range (*n*= 14), and 4.1% in the $175,000 and greater range (*n*= 5).

Among the SSRI-users, the average number of months of antidepressant use was 71.26 (*SD*=3.83). Chi-square tests of independence and ANOVAs were conducted to determine demographic group differences between controls and SSRI-users. Significant between-group differences included SSRI user participants being disproportionately female (62.3% vs. 37.7% of

controls), white (86.9% vs. 67.2% of controls), and older (mean age of 38.26 years vs. 32.10 years in controls). More SSRI user participants also reported being gay (11.5%) or bisexual (13.1%) than control participants (1.6% and 3.3%, respectively). No other significant differences were observed (see Table 1).

2.3 Measures and Materials (see descriptive statistics in Table 9)

SSRI Usage Form. This 5-item self-report measure was developed by the lab to inquire about length, dosage, and brand of SSRI. Sample items include "What brand is your SSRI?" and "What dosage in milligrams do you currently take daily?" Participants also listed any side effects they currently attributed to their SSRI usage. Sample side effects include low libido, weight gain, nausea, difficulty reaching orgasm, or "other."

Beck Depression Inventory. The Beck Depression Inventory (BDI-II; Beck et al., 1996) is a 21-item, self-rated scale that evaluates for clinical depression within the past two weeks. Questions in the measure tap into symptoms of depression, such as suicidal ideation, crying, indecisiveness, loss of libido, guilt, crying, self-dislike, changes in sleep and appetite, irritability, fatigue, sense of failure, and overall mood. Using both cognitive and somatic symptoms of depression, the BDI-II has high test-retest reliability (Pearson r= 0.93) and had high internal consistency in this study (α= 0.94). Each symptom assessed on the measure is ranked in terms of severity on a four-point scale, from a 0 (*not at all*) to 3 (*severely- 'I could barely stand it'*). A total score is then generated by summing the severity ratings for all 21 items.

Beck Anxiety Inventory. The Beck Anxiety Inventory (BAI; Beck et al., 1988) measures clinical anxiety. This 21-item scale evaluates clinical anxiety within the past month. Questions in the measure tap into symptoms of anxiety, such as feeling nervous, fearing death, trembling, heart pounding, and feeling scared. Each symptom is ranked in terms of severity on a four-point

scale, from 0 (*not at all*) to 3 (*severe*). Using both cognitive and somatic symptoms of anxiety, the BAI had high internal consistency for this study (α= .95).

Oxford Questionnaire on the Emotional Side-effects of Antidepressants. The Oxford Questionnaire on the Emotional Side-effects of Antidepressants (OQUeSA; Price et al., 2012) is a 26-item measure of restricted emotions that contains a subsection focused on SSRI use. This questionnaire focuses on four factors of emotion restriction experienced during the past week that can be attributed to SSRI use: 'not caring', 'emotional detachment', 'general reduction in emotions', and 'reduction in positive emotions.' Participants rated their emotionality ranging from 1 (*disagree*) to 5 (*agree*). Sample items include "my emotions lack intensity," "I don't care as much about my day-to-day responsibilities as I did before I developed depression," and "the antidepressant is preventing me from feeling positive emotions." A total score is calculated by summing totals from the four aforementioned subscales. The overall internal consistency reliability (Cronbach's alpha) for this study was .95. Subscale reliability was also high for general reduction in emotions (α=.814), reduction in positive emotions (α=.89), emotional detachment from others (α=.86), and not caring (α=.86). Additionally, the 'antidepressant as cause' subscale was also highly reliable (α=.92).

Demographic Questionnaire. A demographic questionnaire assessed age, sex, race, ethnicity, household incomes, relationship status, sexual orientation, and psychotropic prescription medication use.

Affect Naming Task. The Affect Naming task is a subtest of the Wechsler Advanced Clinical Solutions test of Social Cognition (Pearson, 2009). This task consists of 24 pictures of individuals expressing different facial expressions (i.e., happy, sad, neutral/no feeling, angry, surprised, disgusted, and afraid). Test-takers are asked to choose the correct emotion being

expressed by each picture. Items are scored as a 1 for correct and a 0 for incorrect responses. A total accuracy score is generated by adding up all 24 trials. The internal consistency of this measure was .57 for this study.

Emotional Stroop Task. This color-word task was adapted from the traditional Stroop test in which participants must name colors as fast as they can, read words as fast as they can, and then name the color that words are printed in (inhibit the tendency to read the word) to measure processing speed via reaction time. In the current version, participants were shown 96 words that flashed on the screen in blue, red, green, or yellow ink. The words provided were a mix of 32 neutral, 32 positive, and 32 negative words, such as 'margin,' 'prize,' and 'victim.' These words were compiled from stimulus sets employed in previous studies (Becker et al., 2001; Kitayama & Ishii, 2002; Miller & Patrick, 2000; Paunovic et al., 2002) and were matched for length and frequency of use across groups. In the adapted version, participants were asked to correctly and quickly choose the color of the ink that randomly flashed words were displayed. For example, participants saw the word "label" printed in green and four color choices below the word (i.e., red, yellow, green, and blue). For this example, participants would choose "green." After 10 practice trials, participants viewed 96 words (32 positive words, 32 neutral words, and 32 negative words) in varying colors. Of note, each participant's word order was randomized to reduce order effects. Subjects were told to respond to the color of the ink for each word and identify this color as quickly as possible by hitting the corresponding key on their computer. Reaction time was assessed and compared between emotionally-valenced word groups. Internal consistency for response times were as follows: neutral words (α= .88), positive words (α = .68), negative words (α= .69).

This task was chosen specifically as a measure of executive functioning and processing speed given the emotional content utilized, as past research has shown that serotonin, the primary neurotransmitter being modulated by SSRIs, affects performance on emotionally salient rewards and feedback (Chamberlain et al., 2006). Beyond emotional processing changes, research demonstrates that SSRI use can actually boost other areas of cognition, if it is able to ameliorate the symptoms of depression, rather than cause impairments (Constant et al., 2005; Herrera-Guzman et al., 2010). One study found that acute administration of SSRIs in both control subjects and patients with MDD improved working memory, attention, and executive functioning in both groups (Cassano et al., 2002; Herrera-Guzman et al., 2010) while other studies have documented improved psychomotor speed in patients with MDD (Constant et al., 2005). With this knowledge, it was essential to pick a test that was sensitive to changes in processing of *emotional* information, as SSRI-induced emotional blunting is only known to disrupt emotional responding and was the area predicted to be impacted by SSRI-induced emotional blunting. Given the need to address emotional cognition particularly, the utilization of the Emotional Stroop task allowed for pure reaction time, as measured by neutral words, **and** reaction time with emotional information, as measured by positive and negative words. This task, above others, allowed for comparisons of reaction time in emotional and non-emotional stimuli, which was advantageous and meaningful.

2.4 Pandemic Effects on Study Design

With the onset of the COVID-19 pandemic, there was a civil duty to stop all in-person research to help efforts to stave off the virus. This also became a necessity once CUNY disseminated guidelines to discontinue all in-person research. Thus, several changes were made to this study. Initially, this project (n=11) included assessment of the physiological effects of

SSRI-induced emotional blunting (i.e., respiration rate, skin conductance, and heart rate) which were to be taken after participants viewed emotionally-charged videos (i.e., positive, neutral, and negative). I originally hypothesized that the SSRI-users with emotional blunting would show less physiological change between different emotional valences than both the control group and the SSRI-users who did not report emotional blunting. It was also predicted that SSRI-users who reported sexual dysfunction would show a similar physiological pattern to those reporting emotional blunting. The COVID-19 pandemic forced revisions to change the protocol to a fully remote format, such that physiological measures were no longer tenable. An IRB amendment was submitted in July of 2020 to change the study to a remote online survey format. Dependent variables were thus limited to the Affect Recognition and Emotional Stroop tasks.

3. Statistical Analyses

3.1 Data Entry

All analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) version 27. The primary independent variable for group was coded for SSRI status (0=controls/no SSRI use vs. 1=current long-term SSRI use). For secondary analyses, two variables were used as potential characteristics of emotional blunting. The first was current sexual dysfunction based on endorsement of either decreased sexual desire and/or anorgasmia (0=no, 1=yes). The second measure of emotional blunting was perceived level of "antidepressant as the cause" (0=low, 1=high). Dependent variables (OQUeSA total and subscale scores, Affect Naming task scores, and Emotional Stroop task scores) were entered as continuous variables, including total scores for Affect Naming accuracy and mean response times for each of the Stroop emotional word valence conditions (neutral, positive, negative). To assess moderation, an

interaction term was created by multiplying group status (controls versus SSRI-users) with emotional blunting as measured by OQUeSA centered total score.

3.2 Data Analyses

Means and standard deviations were computed to describe continuous variables, while frequencies and percentages were used for categorical variables. All statistical tests were two-tailed and performed at $\alpha = 0.05$ for interpretation. The chi-square test for independence (Fisher's Exact Test) was used to evaluate between-group differences for the demographic characteristics of sex, race, sexual orientation, current romantic relationship, and annual household income. One-way analysis of variance (ANOVA) tests were used to evaluate baseline differences in age, depression, and anxiety. General linear models were used to determine between-group and within-subject mean differences in scores on the OQUeSA and responses to the Affect Naming and Emotional Stroop tasks. Moderation analysis, as outlined Hayes and Rockwood (2013) using the PROCESS macro for SPSS v.27, was conducted to determine whether main effects of the independent variable (group) on outcome variables (Affect Naming and Emotional Stroop tasks) were affected by the hypothesized moderating variable (emotional blunting as measured by the OQUeSA). Ordinary Least Squares (OLS) regression was conducted through Model 1 in the PROCESS macro for the moderation analyses to calculate the conditional effects of emotional blunting on Affect Naming and Emotional Stroop tasks. Bootstrap samples (n=10,000) and 95% confidence intervals for the conditional effect were used to assess the stability and reliability of moderation models.

3.3 Outlier, Normality, and Assumption Analysis

Data were assessed for skew and outliers and were examined to test the assumptions for analyses utilizing general linear modelling. Box plots, stem-and-leaf plots, normal quantile-quantile (q-q

plots), the Shapiro-Wilk Test statistic, and histograms with superimposed plotted normal curves were used to assess for extreme outliers and to assess for the normality assumption of dependent variables before inferential analysis. Skewness generally within -1 to 1 and kurtosis within -2 to 2 were used as acceptable values to help determine variables' normality assumptions. High skew (-2.26) was observed in scores on the Affect Naming task. After log transformation, skew was reduced to an acceptable level (skew= .16) (Figures 1 and 2). Data were also assessed for homogeneity of variance, heteroscedasticity, and multicollinearity. All assumptions for regression analyses were met. All variables subsequently followed approximately normal distributions without any significant outliers.

4. Results

4.1 Emotional Information Processing

To test the hypotheses that long-term SSRI-users differ in their cognition from control subjects when processing emotional information (Aim 1), ANOVAs were conducted to determine mean group differences in the Affect Naming and the Emotional Stroop tasks. Contrary to the hypothesis that SSRI-users would have poorer accuracy in recognizing emotions than controls (H1A), no differences were observed in mean Affect Naming accuracy scores, $F(1,121)=2.01$, $p=.159$ (Table 2). While it was also hypothesized that SSRI-users would show less variability compared to control subjects in reaction times based on the Emotional Stroop task word valence (H1B), a general linear model revealed no differences between SSRI-users and controls in the mean response times for neutral $F(1,121)=0.01$, $p=.919$), positive $F(1,121)=0.00$, $p=.989$), and negative $F(1,121)=0.03$, $p=.868$) words (Table 2). Moreover, a supplemental analysis determined that SSRI-users demonstrated no within-subject differences in their reaction times to neutral, positive, or negative valence words, $F(2,120)=0.98$, $p=.377$.

4.2 Emotional Blunting

To determine if SSRI-users with emotional blunting differed in cognitive processing of emotional information compared to SSRI-users without emotional blunting (Aim 2), two data analytic approaches were used. To test the hypothesis that long-term SSRI-users who reported emotional blunting would have poorer accuracy in recognizing emotions than long-term SSRI-users who subjectively deny emotional blunting (2A), emotional blunting was first examined as a continuous variable. Hypothesis 2A was not supported; OQUeSA scores were not significantly correlated with scores on the Affect Naming task, $r(61)=.10$, $p=.464$. The second approach transformed OQUeSA scores into an ordinal variable, as cut-off scores for the OQUeSA have not been established, and a slight deviation from normality (skew=0.98) was observed (Figure 3). As such, level of endorsed emotional blunting was re-categorized based on quartiles as "none/low" ($\leq 25^{th}$ percentile, $n=16$), "moderate" ($25^{th} – 74^{th}$ percentile, $n=28$) or "high" ($\geq 75^{th}$ percentile, $n=17$). Results of these general linear models also did not support Hypothesis 2A, as no differences were observed in mean Affect Naming scores between SSRI-users who reported none/low, moderate, or high levels of emotional blunting $F(2,58)=0.89$, $p=.417$ (Table 3). Contrary to Hypothesis 2B, predicting that SSRI-users who subjectively endorse emotional blunting would show less variability in reaction times based on valence of words (positive, neutral, and negative) than long-term SSRI-users who did not report emotional blunting, no differences in mean reaction times on the Emotional Stroop task were observed, $F(2,58)=0.16$, $p=.852$.

4.3 Antidepressant Effects as Perceived Cause of Emotional Blunting

To determine if SSRI-users who attribute their emotional blunting to their antidepressant process information differently than SSRI-users who do not attribute their blunting to their

antidepressant (Aim 3), two approaches were used. Similar to my approach in addressing Aim 2, 'antidepressant as cause' was first examined as a continuous variable based on the total subscale score from the OQUeSA, followed by between-group examinations of the perceived cause subscale score as an ordinal variable. Contrary to Hypothesis 3A, scores on the 'antidepressant as cause' subscale were not correlated with the Affect Naming task score, $r(61)=.03$, $p=.819$. In the second approach, "antidepressant as cause" scores were re-categorized as "none/low" ($\leq 25^{th}$ percentile, $n=23$), "moderate" ($25^{th} – 74^{th}$ percentile, $n=22$) or "high" ($\geq 75^{th}$ percentile, $n=16$). In parallel to the correlational analysis, results did not support Hypothesis 3A as no differences in mean Affect Naming scores were observed, $F(2.58)=0.31$, $p=.736$ (Table 4). Likewise, general linear models revealed no differences in reaction times based on the emotional valence of words presented in the Emotional Stroop task, $F(2,58)=0.93$, $p=.401$.

4.4 Sexual Dysfunction and Emotional Blunting

To determine if SSRI-users who reported sexual dysfunction (i.e., low libido and/or difficultly/inability to orgasm) as a side effect were more likely to exhibit emotional blunting than SSRI-users without sexual dysfunction (Aim 4), ANOVAs were conducted to compare OQUeSA scores. Among the 61 SSRI-users, 37.7% ($n=23$) of them indicated that they had current sexual dysfunction. Results indicated partial support for Hypothesis 4A: that SSRI-users with sexual dysfunction would have higher levels of emotional blunting than long-term SSRI-users who did not endorse any sexual dysfunction side effects. SSRI-users with sexual dysfunction had higher mean scores on the OQUeSA, $F(1,60)=4.03$, $p=.049$, which was driven specifically by their higher scores on the "Not Caring" subscale of the OQUeSA, $F(1,60)=9.93$, $p=.003$ (Table 5). These differences represent a medium effect size for total OQUeSA score (eta squared= 0.64) and a large effect size for the "Not Caring" subscale (eta square = .144).

4.5 Sexual Dysfunction and Emotional Information Processing

Aim 5 was to determine whether long-term SSRI-users who endorse sexual dysfunction process emotional information differently. Hypothesis 5A that SSRI-users with sexual dysfunction (n=23) would have poorer accuracy in recognizing emotions than long-term SSRI-users who do not report sexual dysfunction side effects (n=38) was not supported, $F(1,61)=0.80$, $p=.783$ (Table 6). Support was also not observed for Hypothesis 5B – that SSRI-users who subjectively endorse sexual dysfunction would show less variability in reaction times based on valence of words (positive, neutral, and negative) than long-term SSRI-users who do not report sexual dysfunction. No significant differences were present in the mean response times for neutral, positive, or negative words among participants with sexual dysfunction, $F(1,22)=0.98$, $p=.757$, or among those with no reported sexual dysfunction, $F(1,37)=2.64$, $p=.113$.

5. Discussion

5.1 Study Purpose

The primary purpose of this dissertation was to conduct an original study to elucidate the impact of SSRI-induced emotional blunting in long-term SSRI-users and to determine if individuals with emotional blunting demonstrate cognitive differences when processing emotional information. Furthermore, this study attempted to determine if cognitive differences in blunted individuals could serve as an objective marker of emotional blunting, as it is well known that blunting overlaps with depression and has an insidious onset, making it difficult to accurately detect. Lastly, this study also sought to determine if individuals with sexual dysfunction secondary to SSRI use are at a heightened risk for emotional blunting.

This is an important addition to the literature, as many studies have identified the limitations in self-report regarding emotional blunting, but no study has yet to establish a better

standard in identifying emotional blunting in SSRI-users. Relatedly, the majority of past work on blunting has not set clear exclusionary criteria for depression, leaving room for possible overlap between depression symptoms and emotional blunting. This study excluded individuals with active depression based on a clinically validated self-report measure to ensure that any cognitive differences noted during emotional information processing could be directly attributed to SSRI-induced emotional blunting without the confounding variable of depression. Lastly, there is currently no research on who may be most at risk for emotional blunting, such as SSRI-users with sexual dysfunction. This study evaluated if SSRI-induced sexual dysfunction put users at higher risk for blunting, which has not been previously examined.

5.2 On SSRI Use & Emotional Processing

Contrary to predictions, there were no differences in accuracy of identifying emotions based on facial expressions or reaction times on an Affect Naming task and an Emotional Stroop task between SSRI-users and controls. Because SSRI use has been associated with emotional blunting, I hypothesized that SSRI-users would demonstrate poorer accuracy in recognizing emotions via facial expressions. Similar work has found that women taking oral contraception have poorer emotion recognition due to a blunting of reward responses and alterations in stress response (Hamstra et al., 2014; Hamstra et al., 2016; Pahnke et al., 2019). While it was expected that SSRI-users may exhibit similar difficulty in accurately identifying emotions when compared to control subjects, accuracy differences were not seen in this study. No previous work exists on the association between apathy (SSRI induced or otherwise) and reaction time on Emotional Stroop tasks, but a large body of research supports the concept that individuals respond more slowly on Emotional Stroop tasks when the words are personally relevant. For example, veterans with PTSD demonstrate an attentional bias (slower response due to increased attention) for

trauma-related words (Ashley et al., 2013). This pattern is also present in individuals with clinically symptomatic Obsessive Compulsive Disorder (OCD), where individuals with symptomatic OCD showed attentional bias (slower response) for negatively-valenced OCD words when compared to individuals with remitted OCD (Rao et al., 2010). Additionally, a systematic meta-analysis on Emotional Stroop effects and depression revealed an attentional bias and slower response to negatively-valenced words in clinically depressed individuals when compared to controls (Epp et al., 2012). In sum, the Emotional Stroop task appears to accurately detect attentional bias towards stimuli due to mood or affect changes, with greatest bias and slowest reaction times occurring when stimuli are personally relevant (Wingenfeld et al., 2006). Given that SSRIs have the ability to potentially "numb" and blunt a person's emotions, it was anticipated that blunted individuals would exhibit smaller differences in reaction times based on word valence due to blunting, akin to demonstrating the *opposite* of an attentional bias. However, this study did not capture any differences in reaction times based on word valence (positive, neutral, and negative), nor did it find any differences in overall mean reaction times between SSRI-users and controls. Although the Emotional Stroop task was unable to identify differences in emotional processing, the lack of differences in reaction time to word valence suggests that SSRI-users in this study had adequately treated depression, in line with their BDI-II scores. If SSRI-users were still experiencing depression, slower reaction times to negatively-valenced words would have been captured, as seen in past research (Epp et al., 2012; Wingenfeld et al., 2006).

5.3 On SSRI-induced Emotional Blunting & Emotional Processing

Also contrary to my predictions, there were no differences in accuracy of identifying emotions based on facial expressions or reaction times on an Emotional Stroop task between

SSRI-users who endorsed emotional blunting and SSRI-users who did not endorse emotional blunting. Past research on apathy in Parkinson's disease (PD) established that PD patients with apathy exhibited deficits in recognizing facial expressions of fear, anger, and sadness, above and beyond non-apathetic PD patients (Martinez-Corral et al., 2010). Similar work looking at apathy in Lewy Body disease (LBD) found that higher levels of apathy were correlated with poorer recognition of sad and angry facial expressions (Kojima et al., 2018). With SSRI-induced blunting mirroring apathy, it was expected that individuals reporting SSRI-induced apathy would demonstrate similar difficulty in facial affect recognition experienced by PD and LBD patients (Ho et al., 2020). Contrary to previous work, it was not the case that SSRI-users with SSRI-related emotional blunting had more difficulty recognizing facial expressions of emotions. Likewise, this study did not find any differences in attentional bias and reaction time on the Emotional Stroop task between SSRI-users who endorsed emotional blunting and SSRI-users who did not endorse emotional blunting. It is plausible that cognitive measures just are not sensitive enough to detect subtle differences in emotional processing or that SSRI-induced blunting simply does not impact a person's perception of emotion in their environment. Further possibilities will be discussed in section 5.5.

5.4 On SSRI-induced Sexual Dysfunction & Emotional Processing

Past work has determined that approximately 80% of individuals with SSRI-induced sexual dysfunction also report significant blunting of emotions (Opbroek et al., 2002). In parallel with previous findings, the current study found that SSRI-users who are experiencing sexual dysfunction were more likely to experience emotional blunting, as determined by scores on a measure of SSRI-induced emotional blunting. Particularly, SSRI-users with sexual dysfunction scored significantly higher on the "Not Caring" subscale of the OQuESA. This finding is in line

with the past finding that SSRI-users with sexual dysfunction report less ability to care about others' feelings (Opbroek et al., 2002). Given this established correlation, this study also sought to determine if SSRI-users with sexual dysfunction (low libido and/or difficulties with orgasm) were more susceptible to differences in their ability to process emotional information. While it was hypothesized that individuals with SSRI-induced sexual dysfunction would demonstrate poorer accuracy in detecting facial expressions and less variability in reaction times based on word valence compared to SSRI-users without sexual dysfunction, this study did not capture any differences in reaction times based on word valence (positive, neutral, and negative), nor did it find any differences in overall mean reaction times between SSRI-users with sexual dysfunction and SSRI-users without sexual dysfunction. Overall, it appears that SSRI-users with SSRI-induced sexual dysfunction are more likely to experience emotional blunting, but emotional blunting does not cause a negative impact on a person's ability to accurately and efficiently perceive emotional information.

One of the primary explanations for these results could be that SSRI-induced blunting does not produce changes in basal ganglia-prefrontal cortex circuitry as is in PD, LBD, and depression-related apathy. It is possible that SSRI-indued apathy does not disrupt the aforementioned circuitry in the way disease-correlated apathy does. Instead, SSRI-induced emotional blunting may be better explained by changes in neurotransmitter levels rather than functional deficits in particular brain regions.

5.5 Nonsignificant Results

This study did not find any relationship between SSRI use and cognitive processing, SSRI-induced emotional blunting and cognitive processing, or sexual dysfunction in SSRI-users and cognitive processing. Given this pattern of nonsignificant findings, it is likely that SSRIs do

not alter the way individuals perceive emotional stimuli. Past research has thoroughly documented changes in the way one experiences their own emotions, but seldomly has documented perception of emotional stimuli in one's environment. For instance, a 2003 study looked at changes in facial expression recognition after acute administration of an SSRI via intravenous infusion in healthy adults. Results indicated that individuals who received citalopram were able to accurately detect *more* faces with fear and happiness than their placebo control counterparts, even after only 30 minutes of SSRI exposure (Harmer et al., 2003). While Hamer and colleagues did not look at long-term SSRI use, their results suggest that exposure to an SSRI can have an opposite effect from what was hypothesized here. Similar research on PD and facial recognition also demonstrates inconsistent findings. Argaud and colleagues conducted a meta-analysis on PD patients (who frequently experience apathy) and facial expression recognition and found a lack of consensus in the literature, with some studies citing deficits in emotion recognition and others reporting intact emotion recognition (Argaud et al., 2018). Attentional bias and emotional interference in PD have also been studied using Emotional Stroop Tasks. While some studies note that non-depressed PD patients show differences in their reaction time to Emotional Stroop tasks, most studies found that PD patients with depression are the only ones to demonstrate changes, suggesting that depression is the main underlying factor influencing emotional interference. One study specifically correlated depression and reaction time in PD patients and found that only individuals with the highest level of depression exhibited differences in reaction time to negative stimuli (Serra-Mestres & Ring, 1999). It is thus plausible that cognitive differences as an effect of SSRI use are too small to quantify with the cognitive measures used in this study. Specifically, the Affect Naming and Emotional Stroop tasks may not be sensitive enough to measure cognitive differences in individuals with SSRI-induced

emotional blunting, especially if SSRI-induced blunting does not disrupt circuitries often implicated with apathy in neurological and psychiatric diseases such as the basal ganglia, amygdala, and prefrontal cortex. It is also conceivable that cognitive differences in SSRI-users with emotional blunting simply do not exist. There may be no connection between feeling one's own emotions being blunted and perceiving other emotional stimuli. Without that connection, it is entirely possible that a person who cannot experience happiness, sadness, or anger strongly could still accurately recognize those emotions in others and attend to emotional information equally, regardless of the valence.

5.6 Generalizability of Findings

This study looked at cognitive differences and emotional blunting in long-term SSRI-users to ensure generalizability of findings. In reality, most patients stay on the drug for at least 12 months after recovery for maintenance and some remain on the medication for years due to the long-term nature of depressive disorders, yet most empirical work on SSRI-induced cognitive changes focuses on acute administration of SSRIs (Geddes et al., 2003). This study attempted to fill a gap in the literature by focusing on long-term users to capture differences in the actual target population and provide generalizability of findings. Relatedly, past work has looked at acute administration of SSRIs in healthy control subjects. While this approach reduces confounding variables, it does not capture findings that transfer well to real-world SSRI-users. As such, this study investigated emotional changes associated with SSRI use in actual patients in order to be more generalizable and reflective of real-world outcomes. More needs to be known about long-term effects of SSRI-induced emotional blunting as research suggests that 75% of individuals taking antidepressants are on the medication for at least a year (Hengartner et al., 2020) and the side effect of blunting is often delayed (Reinblatt & Riddle, 2006).

5.7 Limitations

The numerous strengths of this study (i.e., examining real-world SSRI-users, focusing on long-term SSRI-users, excluding depressed individuals, and including diverse ethnicities) are balanced by some limitations. First and foremost, the COVID-19 pandemic necessitated changes to the original study design, including the exclusion of several neuropsychological measures (i.e., assessment of verbal memory for emotional content and verbal fluency). If this study was able to be conducted in person, the ability to utilize additional neuropsychological measures would have allowed for a more complete examination of cognitive changes and assessment of multiple domains of cognition. Because SSRI-induced emotional blunting has significant overlap with apathy in depression, including measures of executive functioning that are already proven to change in depression would be a useful addition, as both depression and SSRI-induced apathy disrupt fronto-limbic networks (Snyder, 2013).

While the Emotional Stroop Task specifically examined speed via reaction times, including tests of other higher order cognitive processes such as set-shifting, impulse control, and cognitive flexibility would provide a deeper examination of executive functioning, which is the domain most susceptible to apathy and depression (Oliver et al., 2019; Shenal et al., 2003). A 2013 meta-analysis of 113 studies of broad executive functioning in depression revealed an association between MDD and neuropsychological performance, such that more severe depression was associated with greater levels of impairment in executive functioning (Snyder, 2013). To provide a more thorough investigation of executive functioning in SSRI-induced blunting, including a pure measure of processing speed (e.g., Trails A), a measure of working memory (e.g., digits backwards), and measures of cognitive flexibility and reasoning (e.g., Wisconsin Card Sorting Task and Trails B) would be beneficial. Along with a more thorough

investigation of executive functioning, it would also have been beneficial to include cognitive tasks that tap into other domains of functioning, such as language and memory. Previous research in depression has established impairment in memory, as learning and initial encoding of information is mediated by frontal lobe systems (Mohn & Rund, 2016). Multiple studies have documented verbal memory deficits in individuals with MDD, particularly for emotionally-valenced information, as individuals with depression exhibit an attentional bias for negative information. This attentional bias is known to enhance memory for negative material and impair memory for positive information (Burt et al., 1995; Dillon & Pizzagali, 2018). Incorporating memory tasks for both emotionally-charged and non-emotional information would be valuable additions to the literature, given that this study is the first to attempt to quantify objective cognitive differences in SSRI-users with emotional blunting. Likewise, incorporating a task of semantic fluency, which is a task of language well-known to be negatively impacted by apathy due to its reliance on frontal subcortical system functioning, would have allowed this study to demonstrate possible language deficits in SSRI-induced emotional blunting (Fossati et al., 2003; Fishman et al., 2017).

Emotional blunting is only newly recognized as a side effect of SSRI use and has been negligibly investigated. Most studies, to date, have attempted to confirm SSRI-induced emotional blunting as a legitimate construct and document it anecdotally rather than looking at ways to objectively identify its presence. The COVID-19 pandemic also forced this study to discontinue all physiological data collection. I originally intended to collect heart rate, respiration rate, and skin conductance on both long-term SSRI-users and control subjects while they were exposed to emotionally charged video and audio stimuli. Looking at physiological responses would be the most objective way of assessing emotional blunting, as it less susceptible to

conscious awareness. While it was hoped that there was minimal conscious awareness of what was being measured during the Emotional Stroop task and the Affect Naming task, it is possible that individuals in the study were consciously aware of the emotional content being presented.

This study would have benefited from a larger sample size with matched demographics. Originally, data from 227 participants were collected. After evaluation of depression based on BDI-II scores, almost 50% of the originally collected sample was excluded due to elevated depression (BDI-II scores greater than 13). According to the National Institute of Mental Health (2019), the typical prevalence rate of depression in the United States in 2019 was 7.8%, a drastically lower amount than the approximately 50% seen in this study. The larger number of individuals with clinically significant depression seen in this study may have been due to the COVID-19 pandemic. Data were collected in July of 2020 when the country was in a state of pandemic-related distress, with no approved vaccinations and uncertainty for the future. After exclusion, this study's SSRI group contained significantly more females, older participants, and more gay/lesbian participants. The SSRI group also only had one Asian participant where the control group had 11 Asian participants. In future studies, matching participants on demographic characteristics would be advantageous to ensure group differences on cognitive tasks were not impacted by demographic variability.

While this study had a notably higher sample of SSRI-users than most previous work, only 17 SSRI-users endorsed high levels of emotional blunting on the OQUeSA. This sample size is comparable with past work, but a larger sample with at least 50 participants reporting high emotional blunting would have been beneficial. To better address the overlap in depression and SSRI-induced emotional blunting and sample size simultaneously, future work should include a depressed group *without* SSRI-induced emotional blunting and a depressed group *with* SSRI-

induced emotional blunting. By including these additional independent variables, future research would be able to capture distinct differences in cognition in depression independently, SSRI-induced emotional blunting independently, and deduce which domains of cognition are susceptible to impact by **both** depression and SSRI-induced blunting. In the current initial work, excluding individuals with active depressive symptomology still on SSRIs was imperative to acquire a "pure" group SSRI-induced blunted individuals without depression. While I would expect similar disruptions given that these syndromes both impact similar fronto-subcortical neural circuitry, it would be meaningful to collect and analyze data on these sets of individuals to determine the level of impact and gather information on moderation effects.

Another limitation of this study was the lack of exclusion of individuals taking oral contraception. This is an issue because oral contraception is known to potentially induce a degree of emotional blunting. For instance, one study found that women taking oral contraception showed blunted cortisol response when being shown emotionally arousing images (Nielsen et al., 2013). Another study found that hormonal contraception blunted reward response and dysregulated the stress response in women resulting in impaired recognition of facial emotion recognition, particularly for negative emotions when compared to naturally cycling women (Hamstra et al., 2014; Hamstra et al., 2016; Pahnke et al., 2019). By removing subjects on oral contraception, a confounding variable would be eliminated; therefore, one would have more confidence that the results and conclusions made about SSRI-induced emotional blunting would be specific to SSRI use alone.

Assessing depression as a condition of state and trait would also be advantageous. The current study utilized the golden standard self-report measure for assessing clinically significant depression (i.e., BDI-II). While clinical depression is seen as a persisting (longer than two

weeks) state of sadness and anhedonia, future work could add another self-report measure of mood, particularly one that can capture state affect to ensure subject's potential elevation in depression is a true clinical disorder rather than a transient negative affect. The Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) is a well-known measure that is used in emotion research and is sensitive to brief fluctuations in mood (Magyar-Moe, 2009). Adding the PANAS in future work would provide greater information on how fleeting emotional state potentially affects executive functioning and overall cognitive performance in individuals on SSRIs.

In designing a study that is conducted in a completely remote fashion, it is difficult to control for engagement and distractors in the environment. Thus, another limitation of the study is that it was not possible to control for participants not engaging in other tasks during the cognitive tasks (i.e., using their phones, having loud noises in the background). While I included attention checks, having participants complete the cognitive tests in person would have ensured proper study engagement and standardized the environment across all subjects.

This study did not examine the effects of SSRI dosage on SSRI-induced blunting, which may be a limitation. Considering dosage in future studies will be beneficial to prescribers, as emotional blunting is a dose-dependent side effect. While dosage of medication is based on individual factors, such as weight and diagnosis, attempting to identify general dosages that make someone most vulnerable to emotional blunting would be critically important to educating prescribers about the frequency and prevalence of emotional blunting. Knowing what dosages are most likely to induce blunting would allow prescribers to heighten their vigilance and potentially probe for the presence of blunting. The onus of detecting emotional blunting truly

falls on the prescriber, as the onset and development is insidious and often is not identified and articulated by SSRI-users (Opbroek et al., 2002).

5.8 Future Directions

While cognitive processing of emotions was not found to be an effective way to measure emotional blunting, the need to identify an objective measure of emotional blunting remains essential to help SSRI-users avoid social disruptions or changes to their daily social functioning. Past work has demonstrated that physiological functioning changes as a function of emotion (Diemer et al., 2016; Lohani et al., 2018) and under the influence of certain drugs ranging from nicotine and marijuana to anti-epileptics (Cooper & Haney, 2009; Lotufo et al., 2012; Valjent et al., 2002). Relationships between viewing emotional pictures or words and changes in cardiovascular and electrodermal responses are well documented (Bernat et al., 2001; Lang et al., 1993). Physiological responses such as heart rate, respiration rate, and/or skin conductance are often relied upon because evoked autonomic or somatic responses occur based on perceptions. In other words, based on one's perception of the situation, the body differentially determines how to appropriately respond physiologically and psychologically (Fujimura et al., 2013). Given that the autonomic system is clearly influential in emotional responding, the study of physiological reactions in the context of SSRI use and emotional blunting may be a viable objective target for future research.

Better understanding of the underlying mechanisms of SSRI-induced emotional blunting should be also elucidated. Research looking at functional changes in the brain in long-term SSRI-users with and without emotional blunting is needed to determine if SSRI-induced emotional blunting affects the brain differently from apathy seen in other neurological and psychiatric populations. Past fMRI studies have focused on changes in emotional processing

with acute administration SSRIs (Takahashi et al., 2005; Tranter et al., 2009). Changes in activation of the amygdaloid-hippocampal regions, orbitofrontal cortex, basal ganglia, and insula were observed when individuals given acute SSRI administration viewed emotionally charged images. Utilizing similar study designs, future work should seek to uncover the functional changes (via fMRI) associated with SSRI-induced emotional blunting to make comparisons to apathy in other contexts. Further understanding of the underlying neural mechanisms of SSRI-induced emotional blunting would inform future work attempting to objectively identify emotional blunting. To isolate SSRI-induced apathy from depression, future studies should continue to exclude individuals with sustained depression, instead of studying individuals on SSRIs for maintenance with remitted symptomatology.

All in all, this is the first study attempting to assess cognitive differences in SSRI-induced emotional blunting and emotional blunting in long-term SSRI-users with remitted depression. While the results suggested that there are no cognitive differences between SSRI-users with and without emotional blunting and between SSRI-users with and without sexual dysfunction, future research considering the functional neural mechanisms behind SSRI-induced emotional blunting may help elucidate better ways to objectively measure its presence. This study furthers the scientific literature by stressing the need for generalizability of findings in long-term SSRI-users and moving beyond self-report for SSRI-induced emotional blunting. To propel the literature on SSRI-induced emotional blunting, future work needs to focus on empirical documentation, neuroanatomical functioning, and subsequent social, physical, and cognitive changes produced by emotional blunting. Additionally, although there were no differences among cognitive measures in this study, this does not mean that future attempts to document differences using other cognitive measures or focusing on physiological changes in SSRI-users with emotional

blunting will not be fruitful. It is possible that the measures chosen in this study were not sensitive enough to capture subtle cognitive changes. Specifically, the Emotional Stroop Task captures lags in reaction time to emotional stimuli which are driven by attentional bias. In past work, the utilization of the Emotional Stroop Task is carefully crafted to make target words personally relevant to the sample group. For example, studies looking at PTSD from active combat often use words like bomb, death, and explosion, as these words contain the emotional salience needed to draw the responder's attention which is known to be the most important factor when creating an Emotional Stroop Task (Wingenfeld et al., 2006). Similarly, studies focused on a sample of individuals with social phobia would alternatively choose words such as stutter, embarrassment, or speech. While the premise of attentional bias remains the same, the words used to cause the bias is not standardized (Wingenfeld et al., 2006). In this study, negative and positive words were chosen from four previously validated Emotional Stroop Tasks. The words chosen tapped into multiple facets of positivity and negativity rather than a specific focus on personal salience. Because personal relevance impacts attentional biases seen in responders, this study may not have captured significant response time differences intra-individually due to the lack of personalization of stimuli. In the future, researchers may consider assessing personal relevance to varying emotional states (e.g., finding what scares someone and using that as negative condition). With this said, tailoring of emotional stimuli may not be applicable in this sample, as SSRI-induced blunting is not inherently emotionally-charged. Indeed, it is the *absence* of emotional responsiveness when one would be typical or expected. Given its *flat* characteristic, using more specific and relevant words may not be possible, as it would be in research on MDD, specific phobias, and PTSD. In fact, research has demonstrated that

individuals with pure apathy (without depression) have decreased salience networks in the brain (Yuen et al., 2014).

Along with salience/relevance issues, the Emotional Stroop Task has been shown to lack test-retest reliability in both healthy control subjects and multiple clinical samples (Dresler et al., 2012; Eide et al., 2002). To address reliability in the future, an Emotional Stroop interference score could be calculated (e.g., reaction time negative – reaction time neutral; reaction time positive – reaction time neutral; and reaction time of all positive and negative – reaction time neutral). By creating interference scores, one could test reliability using the split-half method. While only longitudinal studies with multiple time points can truly address test-retest reliability of the Stroop interference effect, past studies lacking multiple time points have attempted to compare internal split-half reliability to longitudinal findings to ensure reliability is comparable (Dresler et al., 2008; Eide et al., 2002).

To mitigate the limitations of the Emotional Stroop Task, future work may wish to focus on executive functioning more broadly rather than solely in the context of emotional stimuli. Depression is well known to impact multiple aspects of executive functioning such as processing speed, learning and encoding, and organization, even when information lacks emotional charge (Fossati et al., 2003). With these associations well-documented, perhaps future work can expand upon the current study and additionally explore executive functioning with emotionally uncharged information. For example, adding in a list-learning task of words (e.g., California Verbal Learning Test- Version 3) would provide information on memory functioning, but also on subjects' encoding and organization strategies. Along the same lines, future research may wish to examine processing speed outside of emotional words, such as using the Trails A & B tests, to

determine if psychomotor processing speed in SSRI-induced apathy exhibits similar patterns to depression.

In fact, my hope is that this study is one of many future empirical studies to expand upon previous anecdotal reports of SSRI-induced apathy and that this study just begins the journey of using neuropsychological measures to quantify changes in individuals with SSRI-induced emotional blunting. Along with the need to further study SSRI-induced emotional blunting empirically to find quantifiable ways to measure its presence, there is also a need to continue researching the correlation between SSRI-induced sexual dysfunction and SSRI-induced emotional blunting as this study found that individuals on SSRIs with sexual dysfunction are at an increased risk of experiencing blunting. Future work on SSRI-induced blunting might focus on this vulnerable population of individuals taking the drug. Ultimately, this study met its aim of empirically studying SSRI use and its side effects, and it demonstrated the importance of considering ways to quantify emotional blunting beyond self-report.

6.1 TABLES

Table 1
Sociodemographic characteristics in a sample of adults with and without current SSRI use (N=122)

Characteristic	SSRI Use (N=61) *n* (%)	Controls (N=61) *n* (%)	Statistic(df)	*p*
Sex			$\chi^2(2)=14.02$	.001
Male	19 (31.1%)	38 (62.3%)		
Female	38 (62.3%)	23 (37.7%)		
Other	4 (6.6%)	0 (0.0%)		
Age			*F*(1,120=6.67	.011
Mean (*SD*)	38.26 (14.50)	32.10 (11.70)		
Race			$\chi^2(4)=10.18$	.038
White	53 (86.9%)	41 (67.2%)		
Black	4 (6.6%)	5 (8.2%)		
Asian	1 (1.6%)	11 (18.0%)		
American Indian/Native Alaskan	1 (0.9%)	1 (1.6%)		
Other	2 (3.3%)	3 (4.9%)		
Sexual Orientation			$\chi^2(3)=10.01$	.019
Heterosexual	43 (70.5%)	56 (91.8%)		
Gay	7 (11.5%)	1 (1.6%)		
Bisexual	8 (13.1%)	2 (3.3%)		
Other	3 (4.9%)	2 (3.3%)		
Current Romantic Relationship			$\chi^2(1)=0.00$	1.00
Yes	39 (63.9%)	39 (63.9%)		
No	22 (36.1%)	22 (36.1%)		
Annual Household Income			$\chi^2(6)=3.94$	.685
$30,000 or less	15 (24.6%)	11 (18.0%)		
$30,000 – $50,000	12 (19.7%)	7 (11.5%)		
$50,000 – $70,000	10 (16.4%)	13 (21.3%)		
$70,000 – $90,000	7 (11.5%)	10 (16.4%)		
$90,000 – $125,000	7 (11.5%)	11 (18.0%)		
$125,000 – $175,000	7 (11.5%)	7 (11.5%)		
$175,000 or more	3 (4.9%)	2 (3.3%)		
Depression and Anxiety				
BDI-II score, Mean (SD)	6.34 (3.644)	7.29 (3.98)	*F*(1,121)=1.90	.171
BAI score, Mean (SD)	6.82 (6.84)	4.70 (5.21)	*F*(1,121)3.682	.057

BDI-II (Beck Depression Inventory-II); BAI (Beck Anxiety Inventory)

Table 2

Comparisons in Stroop emotional word task and affect naming in adults with and without current SSRI use (N=122)

Characteristic	SSRI-users (N=61) *M* (*SD*)	Controls (N=61) *M* (*SD*)	Statistic(df)	*p*
Stroop response time (msec)				
Neutral	863.55 (170.04)	866.54 (154.15)	$F(1,121)=0.01$	.919
Positive	873.31 (171.58)	872.88 (165.49)	$F(1,121)=0.00$	.989
Negative	860.50 (166.87)	865.20 (143.29)	$F(1,121)=0.03$	.868
Affect naming accuracy	20.13 (3.60)	20.95 (2.72)	$F(1,121)=2.01$	.159

Table 3

Comparisons in Stroop emotional word task and affect naming by level of self-reported level of emotional blunting as measured by the OQUeSA among SSRI-users (N=61)

	Level of emotional blunting				
Characteristic	None/Low (N=16) *M* (*SD*)	Moderate (N=28) *M* (*SD*)	High (N=17) *M* (*SD*)	Statistic(df)	*p*
Stroop response time (msec)					
Neutral	895.68 (160.54)	838.73 (146.36)	920.82 (163.87)	$F(2.58)=1.94$	.153
Positive	877.52 (174.96)	853.56 (158.52)	926.18 (178.84)	$F(2.58)=0.28$	.758
Negative	878.75 (152.28)	849.13 (145.24)	899.85 (132.12)	$F(2.58)=0.36$	.700
Affect naming accuracy	21.33 (1.15)	19.94 (3.64)	19.54 (4.81)	$F(2.58)=0.89$	.417

Table 4

Comparisons in Stroop emotional word task and affect naming by level of perceived "antidepressant as cause of emotional blunting" as measured by the OQUeSA among SSRI-users (N=61)

	Level of emotional blunting				
	None/Low (N=23)	Moderate (N=22)	High (N=16)		
Characteristic	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	Statistic(df)	*p*
Stroop response time (msec)					
Neutral	893.60 (177.44)	822.97 (169.79)	876.13 (158.57)	$F(2.58)=1.03$	.363
Positive	896.64 (165.94)	836.06 (174.97)	890.99 (176.94)	$F(2.58)=0.81$	.449
Negative	885.06 (158.95)	825.46 (181.80)	873.37 (158.59)	$F(2.58)=0.78$	.465
Affect naming accuracy	21.26 (2.09)	20.91 (2.43)	20.56 (3.81)	$F(2.58)=0.31$	.736

Table 5

Comparisons in levels of self-reported blunting among SSRI-users by endorsement of sexual dysfunction (N=61)

	Sexual Dysfunction			
	Yes (N=23)	No (N=38)		
Characteristic	*M* (*SD*)	*M* (*SD*)	Statistic(df)	*p*
Oxford Depression Questionnaire				
Total score	44.17 (19.56)	35.45 (14.27)	$F(1,60)=4.03$	.049
General reduction in emotions	11.78 (5.54)	9.89 (4.42)	$F(1,60)=2.15$	.148
Reduction in positive emotions	12.13 (6.38)	9.71 (4.95)	$F(1,60)=2.75$	.103
Emotional detachment from others	9.04 (5.06)	8.10 (4.14)	$F(1,60)=0.621$	.434
Not caring	11.22 (5.17)	7.74 (3.46)	$F(1,60)=9.93$	.003
Antidepressant as cause	10.74 (5.66)	9.34 (4.51)	$F(1,60)=1.13$	.292

Table 6

Comparisons in Stroop emotional word task and affect recognition among SSRI-users by endorsement of sexual dysfunction as measure of emotional blunting (N=61)

	Sexual Dysfunction			
	Yes (N=23)	No (N=38)		
Characteristic	*M* (*SD*)	*M* (*SD*)	Statistic(df)	*p*
Stroop response time (msec)				
Neutral	884.66 (184.83)	850.76 (161.64)	$F(1,61)=0.56$	.455
Positive	886.84 (191.61)	865.12 (160.39)	$F(1,61)=0.23$	.636
Negative	882.97 (182.54)	846.90 (157.60)	$F(1,61)=0.67$	.418
Affect naming accuracy	20.83 (3.47)	21.03 (2.18)	$F(1,61)=0.80$	.783

Table 7

Effect of emotional blunting as a moderator of SSRI status on Stroop emotional word task and affect recognition

					95% CI	
Model	*Estimate*	*Std. Err.*	*t*	*P*	Lower	Upper
Stroop neutral words						
SSRI status	-3.93	29.57	-.13	.89	-62.49	54.63
OQUESA score	1.24	1.00	1.25	.21	-0.73	3.22
SSRI status x OQUESA score	.17	2.00	.08	.93	-3.79	4.12
Stroop positive words						
SSRI status	-0.73	30.62	-.02	.98	-61.38	59.92
OQUESA score	1.54	1.03	1.49	.14	-0.50	3.59
SSRI status x OQUESA score	-.06	2.07	-.03	.97	-4.16	4.03
Stroop negative words						
SSRI status	-5.53	28.26	-.20	.84	-61.52	50.45
OQUESA score	1.11	.95	1.16	.25	-0.78	3.00
SSRI status x OQUESA score	1.27	1.90	.72	.47	-2.41	5.15
Affect recognition						
SSRI status	-.83	.58	1.43	.15	-0.32	1.97
OQUESA score	-.02	.02	-1.27	.21	-0.06	0.01
SSRI status x OQUESA score	-.01	.04	-0.02	.99	-0.08	0.07

Table 8

Comparisons in levels of self-reported blunting in adults with and without current SSRI use (N=122)

Characteristic	SSRI-users (N=61) *M* (*SD*)	Controls (N=61) *M* (*SD*)	Statistic(df)	*p*
Oxford Depression Questionnaire				
Total score	38.74 (16.85)	38.33 (13.71)	$F(1,121)=0.22$	.883
General reduction in emotions	10.61 (4.92)	10.05 (4.14)	$F(1,121)=0.46$	.500
Reduction in positive emotions	10.62 (5.61)	9.98 (4.27)	$F(1,121)=0.50$	.480
Emotional detachment from others	8.46 (4.49)	9.24 (4.07)	$F(1,121)=1.03$	.313
Not caring	9.05 (4.48)	9.04 (4.10)	$F(1,121)=0.00$	1.00
Antidepressant as cause	9.87 (4.97)	NA*	NA*	

* Control participants were not administered the antidepressant as cause component of the Oxford Depression Questionnaire.

Table 9

Descriptive Statistics of Primary Measures (N= 122)

	Range	Minimum	Maximum	Mean	SD
OQUeSA Blunting Scores	69	20	89	38.5328	15.2977
BDI Total Scores	12	1	13	6.8197	3.82902
BAI Total Scores	28	0	28	5.7623	6.15106
Affect Naming Scores	18	6	24	20.541	3.2042
Stroop: Neutral RT	637.77	549.87	1187.65	865.0311	161.68597
Stroop: Positive RT	698.73	520.21	1218.94	873.0969	167.88233
Stroop: Negative RT	652.97	544.61	1197.58	862.8307	154.99356

6.2 FIGURES

Figure 1

Distribution of Raw Total Scores on Affect Naming Task

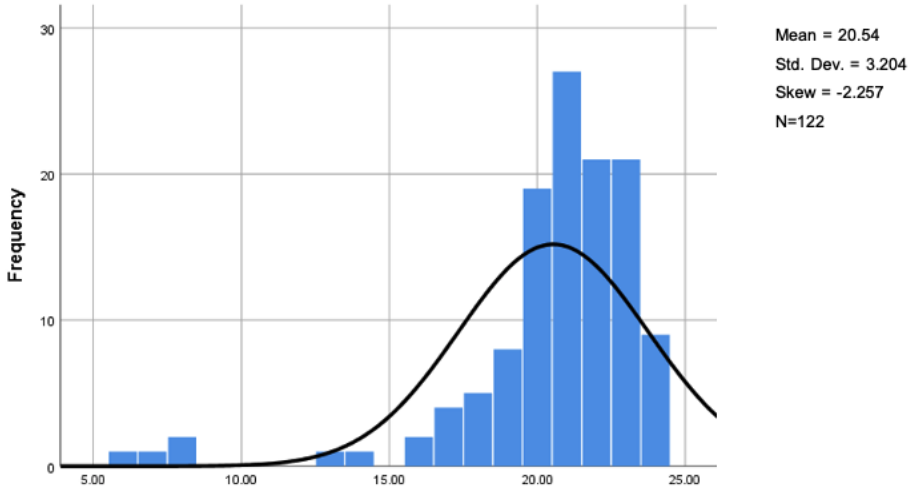
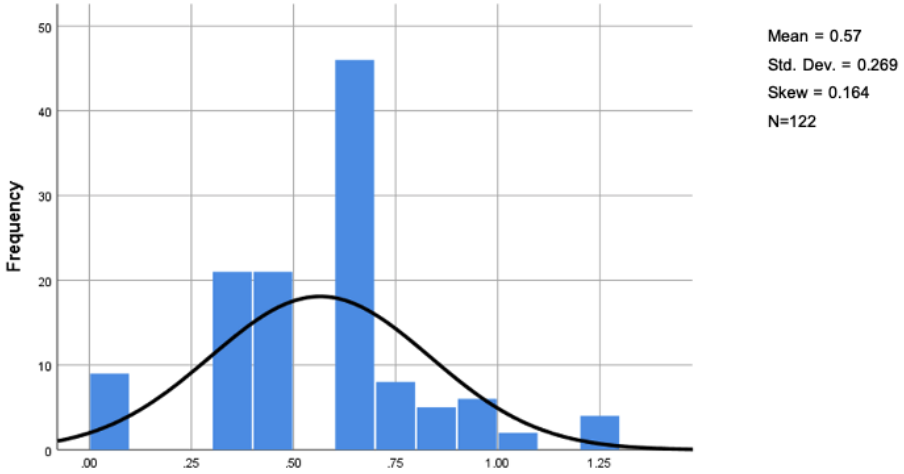


Figure 2

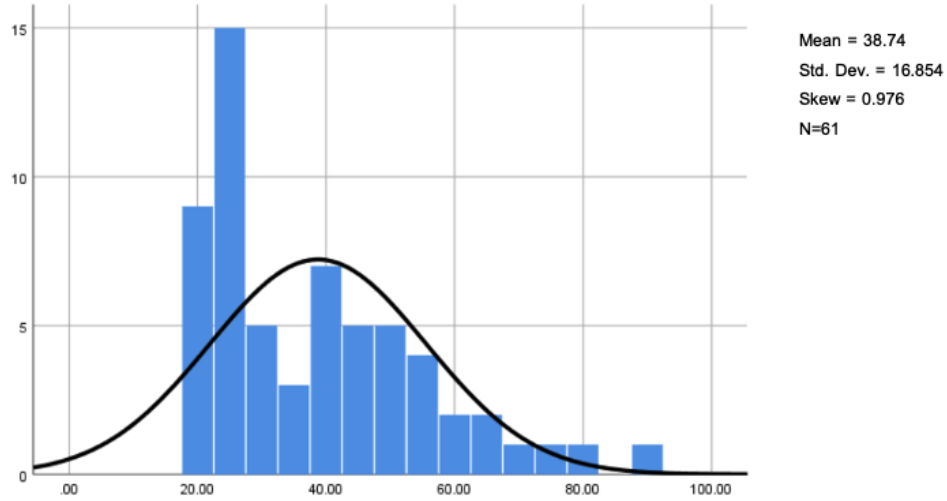
Distribution of Transformed Total Scores on Affect Naming Task



Log10 transformation was used.

Figure 3

Distribution of OQUeSA Total Scores Among SSRI Users



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