Linking anhedonia symptoms with behavioural and neural reward responses in adolescent depression

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Linking Anhedonia Symptoms with Behavioural and Neural Reward responses in Adolescent Depression.

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Highlights:

- **Early onset adolescent depression leads to poorer health outcomes in adulthood**
- **Questionnaires measuring anhedonia in adolescents are needed**
- **Clinical, behavioural and neural measures of anhedonia lack specificity**
- **Effort for reward provides a possible link between brain and motivation**

Abstract:

Adolescence is a period of change that crucially increases vulnerability to depression. Studies report blunted neural responses to reward that relate to positive affect and depression symptoms in adolescents. However how these results relate to the symptom of anhedonia in adolescents is not entirely clear.

Anhedonia is not a unitary construct, but is described as having different processes (e.g. wanting vs. liking) each underpinned by different neurobiological pathways. Current studies report inconsistencies in findings when trying to relate reward processing at the behavioural and neural level with symptoms. One reason for this is the lack of specificity of clinical, behavioural and neural tasks for measuring reward in depression.

Links between the experience of anhedonia in adolescent depression and the behavioural and neural measures of reward could be improved with more detailed questionnaires, more detailed measurements of the components of reward for e.g. decreased motivation/effort and more ecologically valid tasks relevant to adolescents, in the MRI scanner.

Prevalence of adolescent depression

Major Depressive Disorder (MDD) is characterized by persistent sadness, loss of interest or pleasure, feelings of worthlessness or guilt, sleep disturbances, poor concentration and suicidal thoughts. The World Health Organisation reports that depression is the predominant cause of illness and disability for both boys and girls aged 10 to 19 years [1]. As adolescence is a time of physical, social and psychological change, it is easy to see how this could contribute to mental health problems.

Early-onset adolescent depression has a detrimental impact on normal development and leads to poorer outcomes in adulthood. Harrington et al., found that 60% of adults with adolescent onset depression experienced one or more episodes of MDD in adulthood compared to 27% in the control group [2]. Additionally a significant increased risk of later anxiety disorder, nicotine dependence,

alcohol abuse, suicide attempt, educational underachievement and unemployment has been found in adults with early onset depression [3].

As recently reviewed, adult and adolescent depression are clinically very similar with both having depressed mood and anhedonic features [4]. Irritable mood can replace depressed mood as a cardinal symptom of depression in children and adolescents in the Diagnostic Statistical Manual (DSM) [5] but not adults. Though disagreement over irritability as a cardinal mood criterion for depression exists [6] which has led us and others to focus on a key feature such as anhedonia in adolescent depression [4, 7, 8].

Anhedonia in adolescence

Anhedonia one of the key diagnostic criterions for MDD in adults, as recognized by two major psychiatric diagnostic systems: the Diagnostic Statistical Manual (DSM) [5], and the International Statistical Classification of Diseases (ICD) (World Health Organization) and defined as a markedly diminished interest or pleasure in all, or almost all, activities previously enjoyed. Anhedonia has also been suggested as a possible biomarker for depression as it seems to predate depression and persist into recovery [9].

Although there has been much less anhedonia research conducted with adolescents, data suggests that the experience of anhedonia is common in population samples of adolescents [10, 11]. Gabbay et al., using a dimensional analysis described anhedonia compared to irritability, as a hallmark of adolescent MDD as it was associated with greater illness severity, MDD episodes, episode duration, and suicidality [4].

However, scales typically used to assess depression only contain a small number of items on anhedonia such as the Hamilton Depression Rating Scale (HAM-D) [12], which assesses work and interests in 1 item out of 17 and the Beck Depression Inventory Scale (BDI) [13], assesses only 4 items out of 21 (loss of pleasure, loss of interest, loss of energy and interest in sex). Also only 1 item out of the 10 items of the Montgomery–Åsberg Depression (MADRS) Rating Scale (inability to feel: reduced ability to enjoy usual interest, and loss of interest in surroundings, loss of feelings for friends, and acquaintances) appears to try to measure anhedonia [14]. Furthermore questionnaires specifically designed for younger people like the Mood and Feelings questionnaire (MFQ) also only have 2 items pertaining to enjoyment and fun out of 33 and in the short version only 1 item, enjoyment, out of 12 [15]. Therefore there is a severe dearth of clinical measurements of anhedonia for an adolescent population.

The need for anhedonia specific scales for adolescents

There are currently no anhedonia specific measurements designed for adolescents. Most adult assessments use self-report items of pleasure (recently reviewed in more detail here [16]) in response to positive sensory, social and physical stimuli (e.g. Snaith-Hamilton Pleasure Scale (SHAPS) [17], the Chapman Anhedonia Scale CHAPS [18], Fawcett Clark Pleasure Capacity Scale (FCPS) [19]. As these are not designed for adolescents there are perhaps irrelevant questions pertaining to interest in work and interest in sex and an absence of questions related to adolescent life in particular, such as relationships with friends, engagement in social or sporting activities. Interestingly, a recent study finds that the SHAPS does go some way to represent adolescent anhedonia [20]. However the SHAPS nor any of the other measures described above adequately differentiate between various aspects of pleasurable experiences for e.g. the 'wanting' (appetitive/motivation) and the 'liking', (hedonic/consummatory) of reward [21] [16]* [22], making it difficult to examine which components of reward processing are affected in adolescent depression. More recently questionnaires have been developed such as the Temporal Experience of Pleasure scale (TEPS) which attempts to separate the motivational aspects from the consummatory but to date has mostly been used in schizophrenia rather than depression research [23]. Further, the TEPS "anticipation" scale might arguably map onto the ability to "imagine" future events in a positive way [24] rather than capture the motivation to attain those positive events. In the animal literature for example motivation is regarded as appetitive behaviour and mostly measured as the physical effort exerted to achieve a goal [25] (see effort section

below). The Motivation and Pleasure scale, [26] the Anticipatory and Consummatory interpersonal pleasure scale (ACIPS) [27] and the Dimensional Anhedonia Rating Scale (DARS) [28] all attempt to separate components of reward processing, see here for review [16]. Interestingly the DARS asks participants to provide at least two of their own examples of what they find rewarding (e.g. "gardening, playing the guitar" under "hobbies/past-times) which circumvents some of the issues related to age differences in what people might find rewarding (adolescent vs. adults vs. elderly). We have examined the TEPS in adolescents and others have used the ACIP [7, 8, 29] yet still relatively few studies use detailed anhedonia questionnaires such as these in adolescents.

Going forward, questionnaire development is sorely needed that adequately addresses the different components of reward processing in adolescent depression and that also examines specific adolescent anhedonic experiences. One interesting avenue to explore is the questionnaires that have already been developed to measure similar constructs but in a different field. For example in Neurology Parkinson's disease patients are assessed for apathy using measures that may be useful for capturing reward component deficits also seen in adolescent depression. Apathy is described as diminished emotional responsiveness, lack of initiation, interest or participation in daily activities, as reviewed here from this current special issue [30]. Clearly this sounds similar to anhedonia in depression, as reviewed in this current special issue [31] and symptoms of amotivation across diagnostic boundaries [32, 33]. Importantly, apathy can occur without the clinical emotional distress that is seen in depression [34] yet Levy and Dubois claim apathy in depression possibly arises *from* anhedonia which they describe as an insensitivity to pleasure [35]. Yet we now know most studies do not differentiate between the anhedonic experiences of a lack of motivation vs. an insensitivity to pleasure (consummatory component) when they examine reward. Therefore I would argue that measures of apathy used in the field of neurology are useful for examining the lack of motivation/interest component of anhedonia seen in depression. A good example is The Lille Apathy Rating Scale which has 9 sub scales; Everyday productivity, Interests, Taking the initiative, Novelty seeking, Motivation - Voluntary actions, Emotional responses, Concern, Social life and Self-awareness, all relevant to the experience of anhedonia in depression [36]. Furthermore the Apathy Motivation Index (AMI) has been developed to measure subtypes of apathy in behavioural, social and emotional domains that can be used in patients and those with sub-clinical symptoms [37]. It will therefore be of interest to develop these questionnaires further for adolescents and examine across diagnostic boundaries shared and distinct deficits in motivation in adolescents with clinical disorders.

Anhedonia and reward processing in adolescent MDD- behavioural studies.

The nature of anhedonic symptoms has been broadly investigated in laboratory settings, finding that adults with MDD find positive stimuli less positive and less arousing than control subjects [16, 22, 38]. Interestingly, studies that measured hedonic capacity/consummatory experiences in a more direct way by using primary rewards such as tastes of a different sucrose concentration showed that there were no difference in ratings of subjective hedonic experience between MDD adults and healthy individuals, see review [39]. In line with this we have shown that in those recovered from depression [40], in young people with a family history of depression [41] and in adolescents with depression symptoms [7], no subjective differences to the consummation/taste of chocolate reward are detectable, but neural deficits during reward tastes are apparent (see below under Neural section). Therefore it is possible that the lack of differences on hedonic impact of taste may simply be that self-report "liking" scales and the current behavioural measures are simply not sensitive enough to pick up individual differences.

A recent review by Pizzagalli summarises the studies on anhedonia in depression reporting on laboratory-based measures of hedonic behaviour but also reinforcement learning [42]. Pizzagallis group have shown blunted response bias toward stimuli associated with higher monetary reward during decision-making probabilistic learning tasks in adults with depression. Together with work by

Kunisato et al it seems depression is characterized by an impaired ability to modulate behaviour as a function of reinforcement [43]. Interestingly in Pizzagallis study using the subscale of the Mood and Anxiety symptoms questionnaire (Anedonia measured by 8 items AD) they found no correlation between response bias for reward and anhedonia in the MDD group as expected [44]. Though some decision-making studies do find relationships between reward responses and the anhedonia questionnaire SHAPS foe example [45, 46], confusion still remains as to the components of reward it relates to as the SHAPS does not dissociate consummatory components from anticipation or motivation [22, 38]. There are much fewer behavioural studies in adolescents with depression, but reports find that depressed adolescent boys show less distinction between high and low magnitudes of monetary reward during high-probability trials [47]. Further, both adolescent boys and girls with depression show less improvement in cognitive control, measured by antisaccadic eye movements, compared to controls, during a monetary reward task [48]. However this study had only 11 adolescents with MDD and 5 of them had co-morbid anxiety, therefore confounding the contribution of pure depression to cognitive control modulation, reviewed here [49].

Anhedonia and physical effort in adolescent depression

Studies have also begun that assess physical effort expenditure for rewards in adults with depression [38, 50, 51]. For example a recent study in adults examining The Effort-Expenditure for Rewards Task (EEfRT) [52] has found that at low levels of anhedonia, action orientation (a motivation factor) was associated with effort for reward, but this relationship was not present at high levels of anhedonia. Thus, at low levels of anhedonia, action orientation acted as a buffer against stress, but at high levels, anhedonia debilitated action orientation so that it was no longer a promotive factor [53]*. In our recent study with adolescents at high risk of depression compared to controls we also measured effort but using button presses to win chocolate taste and avoid an unpleasant taste using this method we did not find behavioural differences in effort between groups. This may have been due to the small sample size but also that our task required no choice behaviour unlike the EEfRT task [7]. Interestingly, in another study where we also assessed effort but this time by using helping behaviour, we found that adolescents with high depression symptoms were less willing to help others, (pick up papers) compared to controls, in a staged paper dropping task [54]*. Taken together, this recent work investigating effort is a step forward in understanding wanting and motivation in humans and perhaps maps more obviously onto the preclinical work on motivation that involves physical effort in animals [55].

Importantly, studies have begun to use Experience Sampling Methodology which is when participants report their current states of affect, behaviour, and daily context several times a day for multiple consecutive days [56]. Using this method to examine reward processing in young people (16 to 25 yrs.) with a range of depression symptoms, it was found that temporal associations between reward anticipation and both active behaviour and positive affect were reduced with increasing severity of depressive symptoms (measured with MADRS) [57]*. This work is important as it begins to address how different reward processes interact with each other in daily life, therefore improving upon the ecological validity of studies of reward processing in adolescent depression.

Furthermore advances have been made in understanding human behaviour during effort and motivational tasks by using computational modelling this has been reviewed recently here [58]** and in this current special issue [31, 59]. This is a promising new approach able to disentangle processes that underpin the trade-off between effort and reward [58]. In a recent study for example Pessigliones group found that patients suffering from dopamine depletion due to Parkinson's disease were selectively impaired in reward learning, but not effort learning. They also found anti-parkinsonian medication restored the ability to maximize reward, but had no effect on effort minimization. Therefore these results are an important step forward in understanding both motivation processes and the role of treatments in these processes [60]. Going forward this will be an important area to develop in relation to adolescent anhedonia, it would be of interest for example to examine how treatments

like Behavioural Activation [61] interact with effortful reward tasks in adolescent depression, as there are no studies as yet in this area.

Although there are more studies examining anhedonia and reward responses in neural vs. behavioural tasks, confusion between the two domains emerges as the majority of behavioural experiments focus on hedonic/pleasurable aspects whereas neurobiological studies seem to focus on anticipation [38]. Further, neural developmental stages are not always addressed when comparing adults with adolescents across different tasks [62, 63]. Consequently, this only exacerbates the current difficulties, mentioned above, in linking the clinical, behavioural and neural measures of reward and anhedonia in adolescent depression research.

Anhedonia and reward processing in adolescent MDD- Neural studies.

The neurobiology of anhedonia in adult MDD [22, 38, 64-66] and adolescents [49] [67] [68] [69]* has been reviewed in depth already. In summary, studies report mostly decreased responses to reward in adults and adolescents but increased activity also exists. For example both decreased and increased neural activity to monetary reward anticipation and receipt in regions like the caudate and the dorsolateral and medial prefrontal cortex (PFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC) and amygdala has been reported [70]. Additionally, decreased caudate activation during monetary reward anticipation and outcome was associated with lower subjective positive affect measured on the Positive and Negative Affect for Children questionnaire (PANAS-C, with 4 out of 20 items measuring: happy, joyful, energetic, excited) in adolescents with MDD [71]. Although how these effects might be modulated by the symptom of anhedonia specifically is still not clear.

More recently, Stringaris and colleagues (2015) found that adolescents with MDD also had decreased ventral striatal (VS) and middle /medial superior frontal gyrus activity for the anticipation of money but not the receipt of the reward and this was associated with anhedonia [72]. However this study only measured a one item "yes or no" to suffering from loss of interest/anhedonia on the Development and Well-Being Assessment (DAWBA) and therefore could not speak to the various anticipatory, motivational or consummatory components of anhedonia that may have been driving any effects. Interestingly, a recent study found that reward-related neural activity together with structure could predict future substance use in emotionally dysregulated adolescents [73]. Although this study was primarily examining manic symptoms and not anhedonia it is interesting as it aims to link together reward function, the brain and symptoms as a way to predict behaviour. Furthermore, this group also showed that, in youth, future positive mood and energy dysregulation was predicted by a combination of reward circuitry functional connectivity, white matter structure and clinical scores, together explaining 28% of the variance in clinical outcome [74]*. Taken together, studies are emerging that are using both multi-model brain imaging techniques and reward processing tasks to understand clinical symptoms in adolescents.

Event related potentials have also been examined in response to monetary reward and loss in adolescents. Results find that blunted responses in adolescents is associated with illness onset over time and predictions of more depression symptoms [75]. A recent study also examining event related potentials for monetary reward and punishment in adolescent depression, reported delayed neural responses to reward cues and shorter latencies for reward vs. punishment outcomes, compared to controls [76]. Taken together, these results are therefore consistent with the adult depression literature of altered neural responses to reward in depression, but as with other studies in this review these studies did not report on any relationship between their data and clinical measures of anhedonia, which makes it difficult to know if they are reward specific deficits or in fact driven by other symptoms like anxiety.

Frustratingly, not all studies examine how the symptom of anhedonia relates to reward processing, and if they do, they don't always find any correlation between their data, symptoms and what might be expected given the DSM anhedonia criteria. For example Foti et al aimed to use reward processing to subtype depression, Melancholic MDD, characterised by pervasive anhedonia and impaired mood

reactivity to positive events, vs. atypical MDD, characterized by intact mood reactivity. Anhedonia was measured by the MASQ. They found blunted feedback negativity (an event related potential index of reward evaluation) and blunted VS activity to monetary reward in depressed patients characterised by impaired mood reactivity to positive events but this effect was independent of self-reported anhedonia, which did not significantly predict FN amplitude [77]. This finding is interesting as it suggests that the current DSM-defined melancholic and atypical MDD subtypes, do not adequately map onto neural data of reward dysfunction. We can only assume even more studies have found no relationship between reward processing and anhedonia measures and thus fail to report such negative findings. Without consistent examination of the experience of anhedonia and how it relates to behavioural and neural responses to reward, we are left with weak links between current clinical/subjective assessments and the tasks we use to objectively measure them.

As briefly mentioned above we have been examining the link between the components of reward and aversion processing (anticipation of reward or aversion, effort to win pleasant (chocolate) or avoid unpleasant taste (via button presses) and consummation of pleasant (chocolate taste) and unpleasant taste in adolescents [7]. In our recent study we examined a large sample of adolescents (N=84, Yrs. =13-21) with varying degrees of depression symptoms. Using a dimensional approach we found regions such as the pgACC activated to reward anticipation, the insula activated during effort to gain reward and avoid aversion and the medial prefrontal cortex activated during rewarding and aversive taste. However as depression scores (measured with the BDI) increased, neural activity during reward anticipation in the pgACC and during reward taste in the medial prefrontal/orbitofrontal cortex, decreased across all subjects. Whereas, when anhedonia scores (measured with the TEPS) increased, neural activity in the insula during effort to avoid decreased across all subjects (Figure 1) (Rzepa and McCabe 2018 Under revision Jaacap). This is interesting as it highlights the link for the first time between effort, anhedonia and aversion. This suggests motivation deficits have implications not only for missing out on rewarding experiences but also perhaps for increasing the likelihood of negative experiences. We believe this study helps illuminate how different reward components, anticipation vs. effort vs. consummation involve different brain regions and that these in turn are modulated by different symptoms in adolescents.

Some studies have also focused on identifying reward dysfunction as a trait marker for depression by examining those at risk of depression [78, 79]. For example blunted VS responses to happy faces have been reported in young people with a family history of depression [80]. Whilst altered neural responses to reward in regions such as the putamen and insula for anticipation and punishment receipt in the dorsal anterior cingulate cortex, in adolescent females at familial risk for depression [81] has also been reported. Olino et al. similarly reported decreased reward anticipation in the striatum but not consummation for monetary rewards and is the first study to show blunted VS and anterior cingulate responses to social reward in healthy adolescents with a family history of depression when compared with controls [82, 83]. When examining feedback from monetary reward, adolescents with a family history have been found to have reduced VS reward responses compared to controls [84] while studies examining event related potentials for reward also find blunted responses in children with a family history [85]. Our previous study also found that young people at increased risk of depression due to a family history had blunted orbitofrontal and anterior cingulate responses to reward (using sights and tastes) [41], but not ventral striatum which we discussed as either being due to the robust taste stimuli to activate reward or the age of the sample, i.e. being 16 yrs. plus may have been a resilient rather than an at risk group. When examining young people with a genetic link (family history) but no symptomology, the link between the brain and anhedonia may be hard to establish. Using parametric modulations between subjective experiences (wanting, liking and intensity) and the neural response there was a positive correlation with the "intensity" ratings of the reward taste in the dorsal anterior cingulate cortex and anterior insula [86]. Suggesting an increased intensity of experience in those at increased risk of depression compared to controls, interestingly we found no differences in correlations with "wanting" or "liking" [86]. A recent study by Weinberg et al., also attempted to relate experiences of positive affect on a dimensional level with trait markers and neurobiology, they found that lower levels of positive affect as measured by 8 items on the IDAS Inventory of

Depression and Anxiety Symptoms [87] in young people predicted reduced ERP to monetary rewards in siblings, even over and above the sibling's own level of positive and negative affect [88]**.

Interestingly there have also been studies examining how prosocial reward effects depression risk over time. For example Telzer et al. report that adolescents who showed heightened ventral striatum activation during prosocial decisions in relation to donating money to family members experienced longitudinal declines in depressive symptoms over the course of the following year. Whereas, adolescents who showed heightened ventral striatum activation when keeping money for themselves on a prosocial task (i.e., selfish decisions) experienced longitudinal increases in depressive symptoms [89]. This work highlights the importance of context in relation to neural activity. Further a review by Davey et al. reports that frustration gaining social rewards, such as being popular, during adolescence might even lead to suppression of the reward system, eventually resulting in anhedonia [90]. In fact it's been hypothesised that this may be the link between a trajectory from anxiety in young people into depression, as anxiety prevents the seeking out of social rewards [91]. As reviewed by Forbes et al. social rewards are a particularly important class of rewards in depression for e.g. the loss of a romantic relationship has been found to trigger a first episode of depression [92, 93]. Recent work has investigated ecological measures of social reward such as social acceptance and rejection from peers and finds that in adolescents with depression both increased reactivity to negative and blunted reactivity to positive social feedback [94-96]. Furthermore when investigating social status descriptors the same research group recently found hypoactivation in the superior temporal cortex and medial prefrontal cortex, and reduced late activation in the dorsolateral prefrontal cortex and fusiform gyrus to negative (vs. positive) social status words in depressed youth compared to controls. The authors suggest that reduced activity in a "social cognitive brain network" might be implicated in altered interpersonal functioning in adolescent depression [97]. However as important as these studies are in beginning to draw upon more relevant reward stimuli for adolescents (social stimuli) none have examined the relationship between social responses and the subjective experience of anhedonia in any detail, which makes it difficult to determine once again if the findings are reward specific or in fact driven by other symptoms like anxiety.

Conclusion

Taken together, it's clear that there are deficits in both behavioural and neural responses to reward in adolescents with and at risk of depression. However, not all studies measure the symptom of anhedonia and when they do, it may only be measured by one or two items. This approach does not allow the specific anhedonic experiences of adolescents to be captured and related to reward processing components in any detail. Therefore future studies would benefit from the use of more specific anhedonic questionnaires relevant to adolescence that can map meaningfully to reward processing components such as the anticipation, motivation/effort for and liking of rewards. As these currently don't exist, new questionnaires need developing for adolescents, perhaps borrowing items from the field of Neurology where apathy as a lack of motivation is measured in greater detail.

Furthermore, using a dimensional approach to the study of anhedonia, by examining adolescents across the spectrum of symptom severity, should help counteract the current inconsistencies across studies due to different categorisation methods.

Combining detailed measures of the experience of adolescent anhedonia (anticipation vs. effort vs. consummatory measures) with behavioural and neural tasks that attempt to unpick separate components of reward in an arguably more ecologically valid way is also needed. For example measuring monetary reward may not be the most obvious way to tap into reward processing in children/adolescents. Furthermore, measuring effort might be a better way to tap into the amotivation component of anhedonia whilst using primary rewards like tastes or daily social experiences might map better consummatory components. Finally, combining these processes with computational modelling may illuminate the links between clinical, behavioural and neural components of adolescent depression and anhedonia.

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Legend:

Figure 1. Insula activity during Neural Effort to avoid Aversive Taste Correlates with Anhedonia: *left panel*, axial, sagittal and coronal image (-34, -6, 2) z=4.15 $p<0.001$ *right panel*, contrast estimates for insula correlated with anhedonia (TEPS-A).